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# The American Heart Journal

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## Original Communications

### A STUDY OF THE ESOPHAGEAL LEAD IN CLINICAL ELECTROCARDIOGRAPHY\*†

#### PART I. THE APPLICATION OF THE ESOPHAGEAL LEAD TO THE HUMAN SUBJECT WITH OBSERVATIONS ON THE TA-WAVE, EXTRASYSTOLES AND BUNDLE-BRANCH BLOCK

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IN recent years the field of clinical electrocardiography has been extended by the reintroduction of chest leads. The increased use of this type of "unconventional" lead has followed the work of Wood and Wolferth,<sup>72</sup> who found that the standard or indirect Leads I, II, and III sometimes fail to disclose information of diagnostic importance in heart disease. Precordial leads have also been employed in an "exploring" rôle by Wilson and his collaborators<sup>64, 68</sup> in cases of bundle-branch block. There can be little doubt that the utilization of such nonstandard leads has provided a clearer insight into the electrical events occurring on the anterior surface of the heart and has aided in the detection of infarcted areas in the ventricle. On the other hand, the chest leads permit of no more than inferential conclusions as to the electrical events in the left ventricle and disclose no new information with respect to the electromotive changes in the auricular muscle. It has been primarily with a view to investigating the value of the esophageal lead in exploring these regions that the present studies have been undertaken.

The use of the esophagus as a site for the derivation of action currents arising in the heart has had a considerable vogue in animal experimentation. Kraus and Nicolai<sup>27</sup> (p. 85), Rothberger and Winterberg,<sup>51</sup> Selenin,<sup>57</sup> and many others have made use of ano-esophageal leads in dogs. In such procedures the lead has been employed as an axial derivation and not as an exploring method in the more recent terminology of Wilson.<sup>64</sup>

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In the human subject the alimentary route was first used by Waller<sup>60</sup> who placed an electrode in the mouth; but, with the replacement of the capillary electrometer by Einthoven's<sup>15</sup> modification of Ader's<sup>1</sup> galvanometer, this derivation lapsed into disuse. In 1906 Cremer,<sup>10</sup> attracted by the desirability of a closer approach to the cardiac electrical field, reported that he had successfully placed an electrode in the esophagus behind the heart under roentgenological control. He advocated the wider use of this method inasmuch as it permitted of the closest possible approach to the heart in the normal human subject. The following quotation from his paper probably explained why his enthusiasm was not communicated to the profession at large: "Zu meinen Versuchen bei Menschen diente mir hauptsächlich ein Degenschlucker von Beruf der anodisch vorbehandelte Silberelektroden bis zu 10 cm. Länge und 1.5 cm. Durchmesser beliebig in Oesophagus zu plazieren verstand"<sup>10</sup> (p. 812).

In 1934 Lieberson and Liberson<sup>30</sup> revived the method and applied it to six normal human subjects. They used a small German silver electrode and placed it behind the heart under fluoroscopic control. Unfortunately the publication of a typical curve was unaccompanied by a detailed analysis of their material so that it was impossible to evaluate the importance of the method on the data given in their paper.

The investigations reported in the present communication have been devoted to testing the theoretical validity and practical adaptation of the method to human subjects in health and disease. The subject has been treated under two main heads. Part I has been subdivided into the following sections:

1. The application of the method: theory and technic.
2. An analysis of the normal esophageal curves from the human auricle.
3. Observations on the Ta-wave and auricular extrasystoles.
4. An analysis of the ventricular complexes of esophageal leads in normal individuals.
5. Observations on clinical cases of bundle-branch block and ventricular extrasystoles.

Part II, to be published later, is entitled "An Electrocardiographic Study of Auricular Disorders in the Human Subject by Means of the Esophageal Lead."

## PART I

### THE APPLICATION OF THE ESOPHAGEAL LEAD TO THE HUMAN SUBJECT, WITH OBSERVATIONS ON THE TA-WAVE, EXTRASYSTOLES AND BUNDLE-BRANCH BLOCK

#### SECTION I. THE APPLICATION OF THE METHOD: THEORY AND TECHNIC

*Anatomical Considerations.*—As the esophagus passes downward through the thorax behind the trachea, it courses along the right side

of the arch of the aorta and then slightly backward over the root of the lung and bronchotracheal lymph nodes (Fig. 1 *A*). It then runs slightly forward, and about 1.2 to 2 cm. below the tracheal bifurcation it lies directly behind the upper pole of the left auricle (Fig. 1 *B*) in the midline of the body. In its downward course along the posterior surface of the heart (left auricle) opposite the eighth vertebra it begins to deviate to the left and lies in front of the descending aorta (Fig. 1 *C*). As it passes still farther to the left and forward to seek the

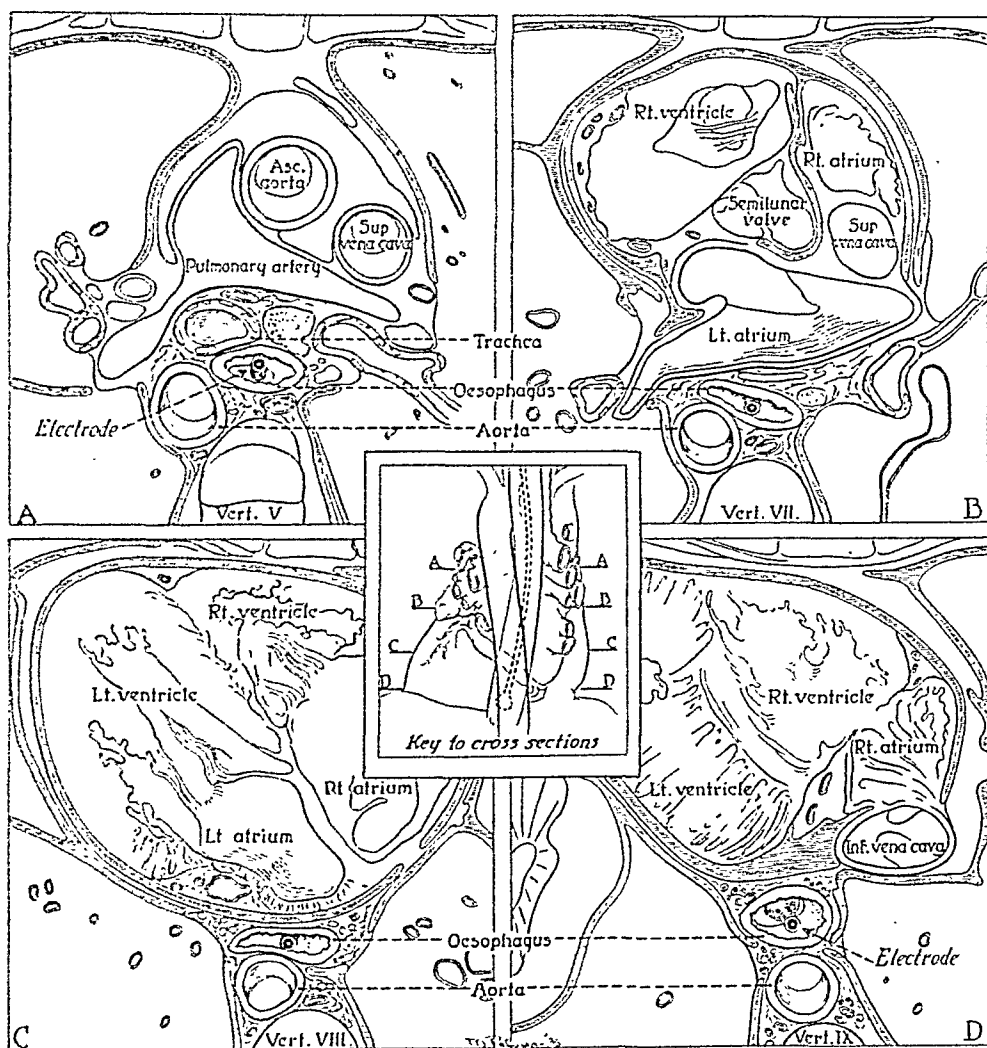


Fig. 1.—Drawings (after Eycleshymer and Schoemaker<sup>49</sup>) of cross-sections of the heart illustrating the anatomical relationship between the esophageal electrode and the heart at the levels indicated in the key drawing.

esophageal aperture of the diaphragm, it passes the lower pole of the left auricle and traverses the posterior or basal portion of the left ventricle (Fig. 1 *D*). Its close cardiac relationships are, therefore, with the left auricle and the left ventricle. The right auricle and the cavae lie to the right and anteriorly at some little distance from the esophagus. The right ventricle lies anteriorly and to the right.<sup>49</sup> Separating the esophagus from the structures enumerated are connective tissue and the layers of the pericardium. During the whole of

its retrocardiac course the esophagus lies close against the pericardium<sup>11</sup> and acts as a sort of sling or hammock to the heart.

*Theoretical Considerations.*—Wilson and his associates<sup>68</sup> have established the theoretical validity of the use of "semidirect" or "exploring" leads. They<sup>69</sup> have shown that curves obtained from an exploring electrode separated from the myocardium by media so constituted as to obey the laws governing the distribution of electrical currents in volume conductors conform to certain mathematical formulae. The soft parts of the body conduct electrical currents according to these laws. In the language of Wilson<sup>64</sup> (p. 613): "It is obvious that an electrode which is placed upon the heart bears no special relation to the subjacent muscle except that of nearness and that there can be no fundamental difference between placing an electrode actually upon the muscle and placing an electrode close to it, provided, of course, that in the second case the electrode is not separated from the muscle by non-conducting substance."

It has been further shown by Wilson and his collaborators<sup>69</sup> (p. 8) "that the potential variations produced by the heart are very large in its immediate neighborhood and diminish rapidly as the distance from it is increased, and that the potential variations of the extremities are, from a practical standpoint, negligible in comparison to those which occur within the heart itself." If the leads are so arranged in a galvanometric circuit that one electrode is close to the heart while the other is placed on the leg, the proximal electrode will be "exploring" or "different," the remote electrode will be "indifferent" and the manner of leading "semidirect." When the exploring electrode is very close to the heart, the potential changes detected by the indifferent electrode are comparatively minute and make no significant contribution to a record so obtained. In other words, the resultant curves are records of the potential variations as they affect the exploring electrode alone.

It has been established by Lewis and his associates<sup>38</sup> that in curves obtained from electrodes placed on the surfaces of the heart, the electrical events may be divided into two types, "intrinsic" and "extrinsic." Intrinsic deflections are those signaling the activation of the small muscle area actually in contact with the electrode. Extrinsic deflections are those resulting from electrical activity in parts of the heart muscle more or less distant from the electrode in question. The distinction is of prime importance since *a determination of the exact time relationships of intrinsic deflections establishes the time at which the explored parts of the cardiac muscle become activated.*<sup>38</sup> Wilson and his coworkers,<sup>64, 68, 69, 70</sup> have been at pains to show by carefully controlled experiments and consideration of the theoretical principles involved that under optimal conditions semidirect leads yield a faithful

representation of the electrical potential variations in the small area of muscle immediately subjacent to the exploring electrode. The essential prerequisites of an efficient or truly reliable semidirect lead therefore demand that the exploring electrode shall be very close to the heart and the indifferent electrode at a comparatively great distance from it. It has been shown that under these circumstances the intrinsic deflections maintain their true time relationships as determined by direct leads within a negligible margin of error.

As an exploring electrode is moved away from the heart, the potential variations recorded by it are quickly reduced in magnitude. The recorded curves are now correspondingly less immune to the potential variations at the site of the remote electrode. Under these conditions the lead becomes less efficient as a semidirect lead inasmuch as curves obtained by it are less faithful records of the potential variations in the previously explored small area of cardiac muscle. The intrinsic deflections are not only of smaller amplitude but also are somewhat distorted by the effect of potential variations at the remote electrode. Such distorting effects tend to disturb the true position of the intrinsic deflections to some extent. Precordial leads suffer from these disadvantages, and, when great accuracy is desirable, certain steps must be taken to exclude distortion due to the remote electrode by making it more truly "indifferent" (Wilson and his associates<sup>67</sup>).

In the light of these established facts it is important to reexamine the relationships of an electrode placed in the esophagus directly behind the heart. Between it and the myocardium are the esophageal wall, the connective tissue attachment, and the pericardium. The connective tissue attachment is of variable length. Near the upper pole of the auricle it is capable, post mortem, of being stretched to an extent of 1 to 2 cm., whereas below, just above the diaphragm, it may, under tension, attain a length of 3 to 4 cm. It should be possible, therefore, greatly to increase the distance between the heart and the electrode. In practice, however, fluoroscopy shows that the esophagus habitually clings closely to the posterior wall of the heart, and the electrode, when in situ, it usually discerned only as a dark object apparently imbedded in the cardiac shadow. This is particularly so when the patient is in a sitting or semireclining posture. Under these circumstances, which prevail in the procedure about to be described, the electrode is almost certainly within 1 cm. and probably within 0.5 cm. of the underlying myocardium.

From what has been stated above, it is clear that an electrode placed in the esophagus immediately adjacent to the heart is in a position to detect the variations in electrical potential occurring in that organ with advantages which cannot be duplicated by any other semidirect lead capable of easy application to the living human subject. It is

separated from the heart by a very narrow but excellent conducting barrier of tissue. Unlike precordial semidirect leads there is no interposition of poorly conducting lung tissue between it and the heart. Above all, the proximity of the esophageal electrode to the source of changes in electrical potential reduces the possible interference of the distal or indifferent electrode to negligible proportions and obviates the necessity of special measures to combat distortion attributable to that cause.

This conclusion was put to a simple test:

A dog weighing 13.2 kg. was anesthetized with dial and urethane (Ciba: 0.6 gm. per kilogram). The right auricle was exposed by a sternum-splitting operation and pericardial incision. To a point near the base of the right auricular appendix a kaolin-saline copper-sulphate electrode bearing a strand of fat-free wool (direct "nonpolarizable" electrode) was attached by a stitch. The strand of wool was insulated, except at its attached tip, by a thin rubber cover. The free ends of the thread of the affixing stitch were carried through the pericardium and then through a pad of lint 0.7 cm. in thickness saturated with normal saline solution. A silver esophageal electrode was then tied to the outer surface of the lint pad by the free ends of the original stitch thread. In this way the esophageal or semidirect electrode was superimposed upon the direct electrode and both were in a position to tap the electrical potential changes occurring in the small area of auricular muscle bearing the stitch. Each of these electrodes was attached to separate right arm terminals of a two-stringed Cambridge galvanometer, and the circuits were completed by attaching the left leg terminals to the left hind leg of the animal. By this arrangement electronegativity of the exploring electrodes was indicated by an upward deflection in the records so derived. Conventional Lead II was attached to a single-stringed Hindle galvanometer from which the light was projected by prisms to a 12 cm. camera common to all three string shadows. The circuit resistances were balanced. In this way a triple simultaneous record was obtained of an indirect Lead II, a semidirect lead with a metal esophageal electrode, and a direct nonpolarizable lead.

Figure 2 illustrates the result of this experiment. This curve has been subjected to a comparator analysis by which it was found that the onsets of the sharp upstrokes or intrinsic deflections of the auricular complexes exactly coincided in both semidirect and direct leads. The experiment, which has been successfully repeated on four different animals, is, with minor variations, a repetition of the work of Wilson and his coworkers,<sup>68</sup> and the results entirely confirm their views with regard to semidirect leads when the electrode is close to the heart. It has an additional interest from the point of view of the present problem in that the same type of metal semidirect electrode was used in these experiments as was used in the investigations on the human subject in the series about to be described. The same method of procedure has been followed with regard to the ventricle, to which reference will be made in the later part of this paper. In neither instance has there been any evidence of distortion of the curves as obtained by the semidirect method due to polarization effects (*vide infra*).

*The Clinical Application of the Esophageal Lead*

In consequence of the conclusions reached on theoretical grounds, a study of 142 human subjects by the esophageal lead was undertaken. The subjects fell into the following groups:

Normal control series	15
Those with cardiac disease	127*

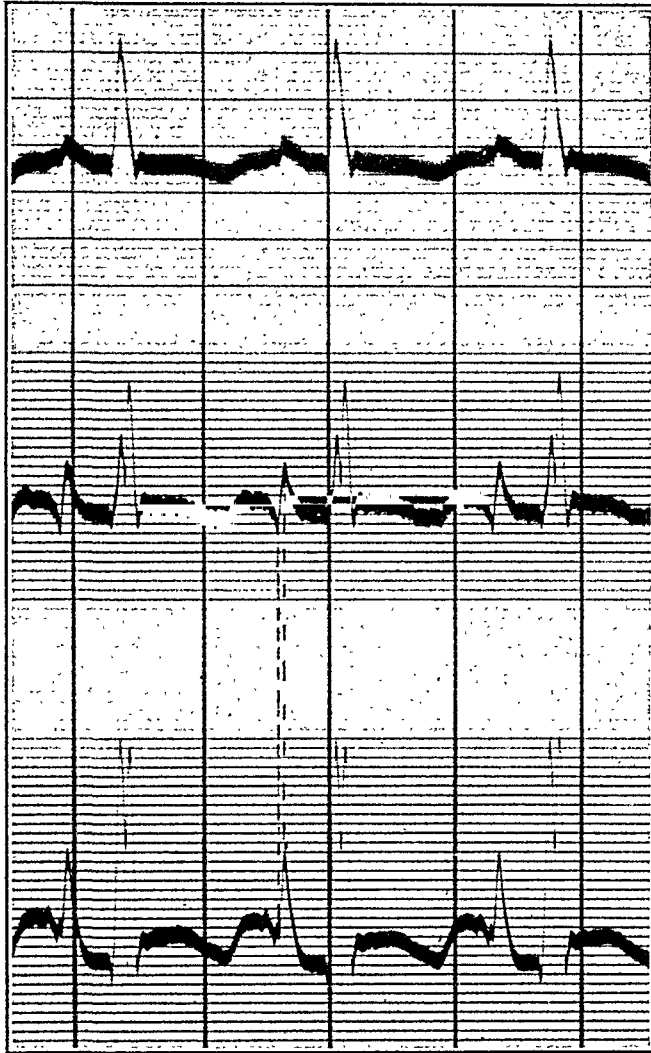


Fig. 2.—Simultaneous records from the experiment described in the text. The upper record from indirect Lead II; middle record, direct lead from the surface of the auricle; the lower record from a semidirect lead placed exactly over the area tapped by the direct lead. The intrinsic deflections are the sharp upstrokes in the auricular complexes in the two lower records. They are exactly coetaneous. The camera is at double speed; the time marker (vertical lines) indicating intervals of 0.2 sec.

Standardization of Lead II, 1 mv. = 10 mm. In the direct and indirect leads the standardization was unfortunately not recorded but is about one-third and one-half of normal sensitivity, respectively.

\*The 127 abnormal cases have been classified in accordance with their outstanding cardiac manifestations as follows:

Discussed in Part I.	Complete heart-block	5
	Auricular extrasystoles	7
	Bundle-branch block	14
	Ventricular extrasystoles	9
	Second degree heart-block	3
Discussed in Part II.	Aortic insufficiency (syphilitic)	2
	Hypertensive heart disease	28
	Myxedema	4
	Rheumatic heart disease	24
	Auricular tachycardia	4
	Auricular flutter	4
	Auricular fibrillation	21
	Miscellaneous	2



*The Method.*—With the subject in a sitting or semireclining position the pharynx is sprayed with 5 per cent butyn solution. During this procedure the subject is instructed to inhale deeply two or three times and then to swallow. From three to five minutes later a subjective numbness or “wooden” sensation in the lower pharynx is indicative of an adequate degree of local anesthesia. The electrode is then passed in the usual manner.

*Description of the Electrode.*—The electrode consists of a small pear-shaped solid silver or German silver mass attached to a partially annealed German silver wire which is in turn covered by a thin soft rubber tube.

The following are the dimensions which were found to produce the most satisfactory electrode:

*The pear-shaped silver mass:*<sup>2</sup>

Length (including flange)— $3\frac{3}{8}$  in.

Diameter of widest part (lower end)— $5\frac{1}{16}$  in.

Diameter of middle part— $3\frac{1}{16}$  in.

Diameter of small flange at upper end for attachment of the insulating rubber tube— $3\frac{1}{32}$  in.

*The German silver wire:*

Diameter— $\frac{1}{40}$  in.

Length—about 24 in.

*The rubber tube:*

Diameter (outside) about  $3\frac{1}{32}$  in. or less.

Length—20 in.

The solid silver mass is canalized in the center from apex to base to admit the wire. In the center of the base a small silver screw is made to fit into a countersunk depression. The wire is led in from the apex, and the end is securely fixed by the screw into the countersunk base. All sharp surfaces on the silver mass are carefully smoothed. The insulated rubber covering is securely tied to the apical flange and to the wire near its free projecting end. The rubber tube is marked in centimeters between the distances 25 to 45 cm. as measured from the widened lower end of the pear-shaped silver mass. The base of the truncated cone of the silver ball is downward when the electrode is introduced, thus minimizing discomfort both in swallowing and upon withdrawal.

*The Technic of Passing the Electrode.*—The operator stands on the right side of the patient holding the insulated wire in his right hand. The silver ball is placed on the dorsum of the tongue. The subject, in a sitting position, is instructed to hold the chin well in and to take two successive quick swallows with the teeth held apart. As this is done, the insulated wire is gently but rapidly passed through the fingers so that the electrode slips in the course of a few seconds to a depth of about 20 cm. from the teeth. He is then told to take three or four deep breaths by mouth and again to swallow. In this way the electrode in less than ten seconds reaches a depth of about 30 cm. and lies below the level of the bifurcation of the trachea, thus obviating any tendency to cough. A few deep breaths at any juncture will abolish “gagging” after the larynx has been passed.

There is no need for haste in subsequent steps. The effect of butyn is dissipated in some fifteen to twenty minutes, but in this series no undue discomfort was encountered when, in some of the experimental procedures, the electrode was retained in situ for as long as one hour.

<sup>2</sup>In a new electrode of the same dimensions all except a narrow band of the widest portion is insulated. Full tests of this electrode have not yet been completed, but polarization effects are considerably increased.

*Fluoroscopic Control of the Position of the Electrode.*—In ambulatory patients the next step is to determine the relationships existing between the depth of the esophageal electrode and the cardiac chambers. By using orthodiascopic technic throughout, the positions of the electrode are marked on a line drawing of the heart in terms of depth in centimeters from the teeth. It is best to begin with the electrode in position just above the diaphragm behind the base of the left ventricle. This particular position is easiest determined with the patient in the left anterior oblique position. The patient is then placed in the right anterior oblique position, and the electrode is pulled up a few centimeters at a time in successive stages and held in position by pressure of the teeth while the determinations are made. In this manner the depth of the electrode is known for each position, and the electrode can subsequently be replaced at the several points without resort to the fluoroscope.

*Determination of the Position of the Electrode When Fluoroscopic Control Is Impossible.*—As 22 of the series of 142 subjects were not well enough to undergo fluoroscopic examination, an additional measurement was made in all cases of the series in an attempt to acquire some other guide to the position of the electrode. With the patient in the sitting posture and the angle of the jaw horizontal, the distance from the tip of the thyroid cartilage to the top of the ensiform cartilage was measured. A comparison was made between these measurements and the depth reading on the graduated esophageal electrode and the known positions of the electrode with respect to the heart. Averaging the results in which fluoroscopic control was available, it was found that multiplication of the measurements in centimeters (tip of thyroid cartilage to the midriff) by the factor of 1.33 always indicated the depth in centimeters requisite to bring the electrode behind the left auricle. The measurement thus obtained seemed to be of more value, in that it was less arbitrary, than that of Minkowski<sup>44</sup> (35 to 37 cm. from the teeth).

*The Galvanometer Leads and Method of Recording.*—After an exhaustive comparison of all possible combinations of the esophageal lead with indifferent points, including the front and back of the chest as well as the conventional sites, it has been decided as a routine procedure to use an axial lead roughly comparable to standard Lead II. The right arm terminal of the galvanometer is attached to the projecting free end of the wire from the esophageal electrode and the left leg terminal to the left leg. *Curves taken in this manner indicate electronegativity of the right arm terminal by an upward stroke on the record.*

The electrode is placed in the position found by fluoroscopy to be just above the diaphragm and behind the left ventricle. The patient is instructed to swallow with the teeth clenched to ensure that the electrode has passed to its full depth. Successive records are then taken. Between each record the electrode is pulled up 1 or 2 cm. and held in position by the teeth. By proceeding in this manner, the whole of the posterior and postero-inferior surfaces of the heart may be

traversed in the esophageal plane until the electrode passes above the upper limits of auricular tissue. In this series six or more such records have been taken as routine, but three are usually sufficient for most purposes. Immediately after or before these records are taken, the conventional Leads I, II, and III are obtained for comparison.

At the conclusion of the operation the esophageal electrode is withdrawn by swift but gentle traction, washed, sterilized and placed in a graduate of distilled water until further use.

### *Comment on Detail*

*Difficulty With the Compensating Resistance.*—In many of the newer galvanometers insufficient adjustable compensating resistance is included in the control box. It is manifest that greater compensation may be required under the conditions of procedure (one electrode internal and the other on the skin surface) than with conventional leads. When it is found impossible, as sometimes is the case, to bring the string back in front of the camera with the lead circuit fully thrown in, two adjustments may be made. The first is to reapply carefully the skin or indifferent electrode. The second is to readjust the standardization of the compensating current so as to permit a deviation of 15 degrees instead of the usual 10. This maneuver gives a 50 per cent increase of the available E.M.F. in the compensating circuit but, of course, necessitates a revaluation on that basis for each millivolt step in the adjusting resistance in the control box. The difficulty never arises in the older instruments in which a sufficient range of adjustable compensating resistance is available.

*Polarization of the Electrode.*—All electrodes used in electrocardiography are subject in some degree to polarization, and this is particularly intensive when small metal electrodes are used.<sup>48</sup> Because unduly large degrees of polarization cause serious distortion of electrocardiographic records,<sup>31</sup> it is necessary to examine the esophageal electrode from this point of view.

Before the above described method was adopted, repeated tests for polarization of the esophageal electrodes were made according to the procedure followed by Pardee.<sup>48</sup> One end of a bandage saturated with normal saline was arranged to enwrap the esophageal electrode, and the other was placed against the contact face of a German silver leg electrode 5.5 cm. by 3 cm. in dimensions. The two electrodes were then connected with a Hindle galvanometer and successive one millivolt additions or subtractions of the compensating current were made. The string was loosened sufficiently to obtain a 1 cm. deflection for each millivolt in the presence of about 2000 ohms resistance in the testing circuit.

Figure 3 illustrates the results of four such tests. Record 3 *a* shows the deflection of the string when a resistance of 2000 ohms was substituted for the testing or electrode circuit. It is to be observed that the string has been purposely left loose to obtain the full effect of polarization in the subsequent records 3 *b* and 3 *c*. Record 3 *b* is a record of standardization curves with the esophageal and leg elec-

trodes in the galvanometer circuit. The curves of record 3 *c* show the degree of polarization obtained when a second leg electrode is substituted for the esophageal electrode. Record 3 *d* illustrates the effect of adding sufficient hydrochloric acid to the saline to bring the acid concentration to about 0.3 per cent. The circuit in this instance is arranged as in 3 *b* (esophageal and leg electrodes) but the string has been made less sensitive, and this somewhat masks the increase of polarization which occurred.

In the clinical use of the method a higher degree of polarization than is illustrated in record 3 *b* has not often been encountered. Occasionally in the lower positions of the esophageal electrode a marked drifting of the string in one direction and a considerable disturbance of the standardization curve have been observed. It is possible that these

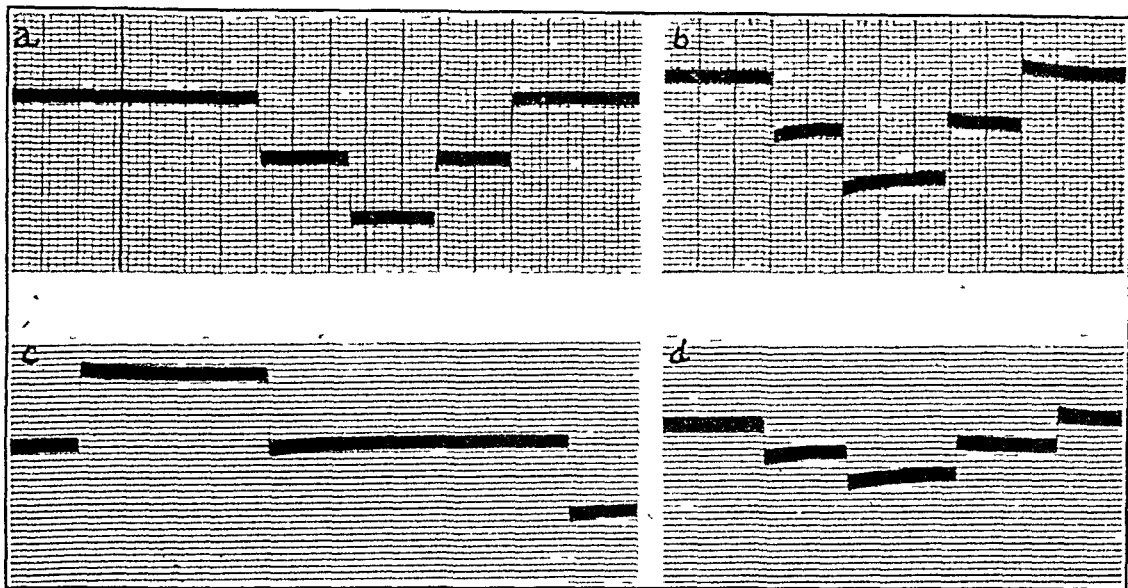


Fig. 3.—For details see text. Records *a*, *b*, and *c* are taken with the galvanometric string standardized so that 1 mv. = 9 mm. in the presence of 2000 ohms resistance. Record *d* is taken with the string sensitivity reduced to one-half this amount.

are due to regurgitation of acid stomach contents into the lower esophagus. After a few seconds the drift of the string becomes negligible although distortion of the standardization curves still, of course, remains. It is possible even in these circumstances to obtain fairly presentable curves, but there can be no doubt that they are considerably distorted.

The way in which such curves are modified by polarization requires some comment. There is interference both with the recorded amplitude and to a slighter extent with the time relationships of the more rapid changes of potential and, in particular, the returning stroke from any sharply developed peak. The above observations have been directed only to the instances in which an unduly large polarization effect is noted, and it should be emphasized that such instances are comparatively rare. Since, however, the method is subject to this disadvantage

in some degree, it is likely that detailed comparisons from case to case with respect to amplitude may lead to fallacious conclusions. On the other hand, comparisons based on the time relationships of particular deflections in the same record or in different records from the same patient are valid unless there is clear evidence of a gross change in the degree of polarization.

A large group of patients have been examined at repeated intervals, and in these comparator analyses of the curves obtained from the same esophageal sites in the same individual have shown a high degree of fidelity even to the minute details of the compared records. This is considered to be substantial evidence that the slight degree of polarization illustrated in Fig. 3 is not of a grave character. In an earlier part of this paper (Fig. 2) experimental evidence has been offered in further support of this contention. For these reasons it has been concluded that, although admittedly not entirely free from polarization effects, the electrode and the method as described may legitimately be applied to electrocardiographic investigation in the living human subject.

*Phasic Deviations of Extraneous Origin.*—In some patients, especially with low lying positions of the electrode, marked phasic deviations of the base line may occur. These may be very great if the electrode is in the sphincterlike diaphragmatic opening. In other positions they are chiefly due to respiratory interference. It is advisable, therefore, to have the patient arrest his breathing for the requisite time during the actual recording. Swallowing or coughing will also affect the curves.

*String Standardization.*—Except when otherwise stated, in all the records reproduced in this paper the string standardization is the same in the esophageal and conventional lead (1 mv. equals 1 cm.). It is expedient to restandardize the string for each new position of the electrode.

*Contraindications to the Use of the Method.*—Apart from patients with actual disease of the pharynx or esophagus (tumors, diverticulae, infection, abscesses, etc.) and patients who are critically ill or are vomiting, there are no contraindications to the method. Butyn is bitter to the taste; so it may be taken as a guide that if a patient who is ill cannot tolerate the mere spraying of the throat, it is useless to attempt to proceed. It should, however, be emphasized that the passage and retention of the electrode, as outlined above, occasions less discomfort and is better borne than similar procedures with duodenal or small stomach sampling tubes.

In the entire series no prolonged attempt was made to introduce the electrode. On only two occasions was the initial attempt unsuccessful.

ful; both were in psychoneurotic patients. In all other instances the electrode was successfully and easily passed in less than fifteen seconds.

### *Summary of Section 1*

1. The anatomical relations of the esophagus to the heart chambers are indicated.

2. An electrode in the esophagus behind the heart is an "exploring" or "semidirect" electrode. The theoretical considerations relating to the use of an esophageal electrode as a semidirect lead in clinical electrocardiography are reviewed, and experimental evidence is offered in support of the conclusions reached.

3. The method is described in detail and the clinical cases to which it has been applied are enumerated.

4. Certain difficulties, including polarization of the electrode, are discussed.

5. The conclusion is reached that on both theoretical and practical grounds the method may legitimately be applied to electrocardiographic studies of healthy and diseased conditions in the living human subject.

## SECTION 2. AN ANALYSIS OF THE NORMAL ESOPHAGEAL CURVES FROM THE HUMAN AURICLE

In Section 1 of this paper evidence has been offered to prove that records obtained by the use of an esophageal electrode may be considered to be essentially the same as those obtained by a direct lead. For this reason it is proper to refer to esophageal curves as "electrograms" as distinct from "electrocardiograms" as obtained by indirect leads. The distinction is made in the interests of clarity, for it is obvious that a curve obtained by the esophageal method is not primarily a record of the currents of action of the heart as a whole since the heart does not lie between the two derivative electrodes. Such a curve is rather a record in which all cycles of activity of the heart are indicated but in which disproportionately great emphasis is placed on the changes of potential in one small region of cardiac muscle lying immediately adjacent to the exploring electrode.

Before proceeding to a consideration of the findings in disease, it is desirable to determine the character of esophageal electrograms in the normal human subject. To this end fifteen normal controls were examined by the method. The ages of the members of this group ranged from twenty-two to fifty-eight years. The findings obtained when the exploring electrode was lying close to the auricle will first be reviewed.

*The Auricular Complex.*—Figure 4 A recalls the general relationships of the esophageal electrode to the human auricle. The drawing represents the posterior surface of the heart. The esophagus is shown

overlying the left auricle and the base of the left ventricle. It is seen that normally the esophagus does not come into contact with the right auricle nor the venae cavae although it is quite possible that rotation of the heart and possibly enlargement of the right auricle may bring these structures into a closer relationship. The upper and lower limits of the left auricle are indicated by broken lines.

In Fig. 4 B, the curves *A* to *H* are those obtained from the correspondingly lettered positions of the electrode indicated in the drawing (Fig. 4 A). In positions *C* to *G*, inclusive, the electrode lies behind the

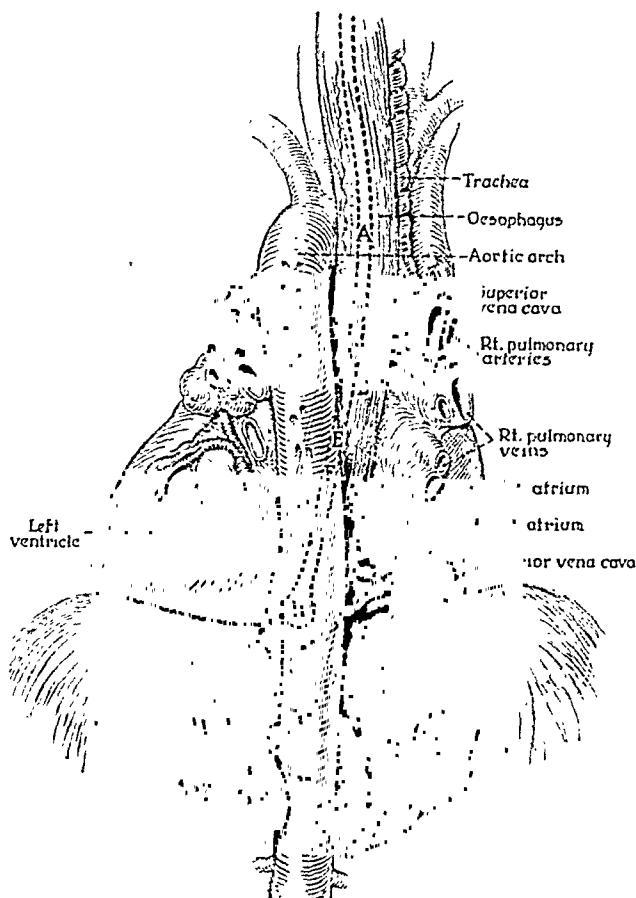


Fig. 4A.—Drawing of a posterior surface of the human heart to illustrate the position of the esophagus in relation to the left auricle and the left ventricle. The lettered areas indicate the regions tapped by the electrode. See Figure 4B.

left auricle. In these curves the P-waves have a polyphasic character. If they are examined more closely, it is apparent that they exhibit differences, the most pronounced of which concern the main upward stroke. In curve *D* this stroke occurs very early in the complex, whereas in *G* it occurs much later. It is also noteworthy that the P-waves of records *A* and *B*, obtained from positions above the level of auricular tissue, are of very different character from those just mentioned, and that *A* is very like the conventional Lead II. These curves (*A* and *B*) differ from the others (*C* to *G*) in the complete absence of any sharp upstroke.

The sharp upstroke is, therefore, obtained only when the electrode is very near auricular tissue. As already stated, such upstrokes indicate electronegativity of the small region of myocardium immediately subjacent to the electrode.

In the experiment which provided the data for Fig. 5, a double esophageal electrode was used. The principles of construction were the same as those described above except that a hole was bored in the center of the upper silver ball to permit the passage of the insulated

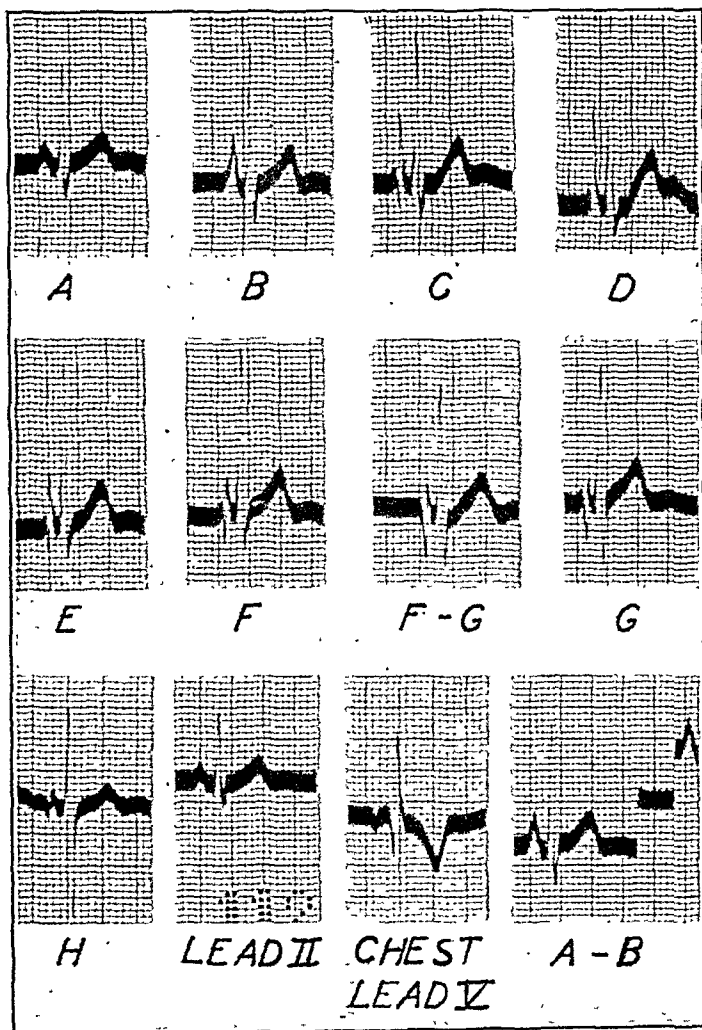


Fig. 4B.—Subject, a normal student, aged twenty-three years, illustrating the esophageal electrograms obtained respectively from the areas indicated by letters in Fig. 4A. Lead II and chest Lead V are included for comparison. Standardization for all curves is shown in record A-B which also demonstrates that polarization is a negligible factor. For full discussion see text.

NOTE.—The heavy vertical lines in the curves mark the time in 0.2 sec. intervals. This is true of all illustrations in the paper. In many instances as in the curves here reproduced a further subdivision into time intervals of 0.04 sec., has been made.

wire from the lower electrode. The distance between the electrodes was 4 cm. Each esophageal electrode was attached to one of the right arm terminals of a two-stringed galvanometer. The left leg served as the site of the remote electrode or indifferent lead in both circuits. Simultaneous records could thus be taken from two different points on the auricles.



The line drawing of the heart in the right anterior oblique position indicates the relationship of the two electrodes to the left auricle (crosshatched) as determined by fluoroscopy.\* The records taken simultaneously from these two points are shown immediately adjacent to the drawing (curves marked *A* were obtained from electrode 1 and curves marked *B* from electrode 2). Each of these curves is also shown taken simultaneously with Lead II, care being taken to avoid any

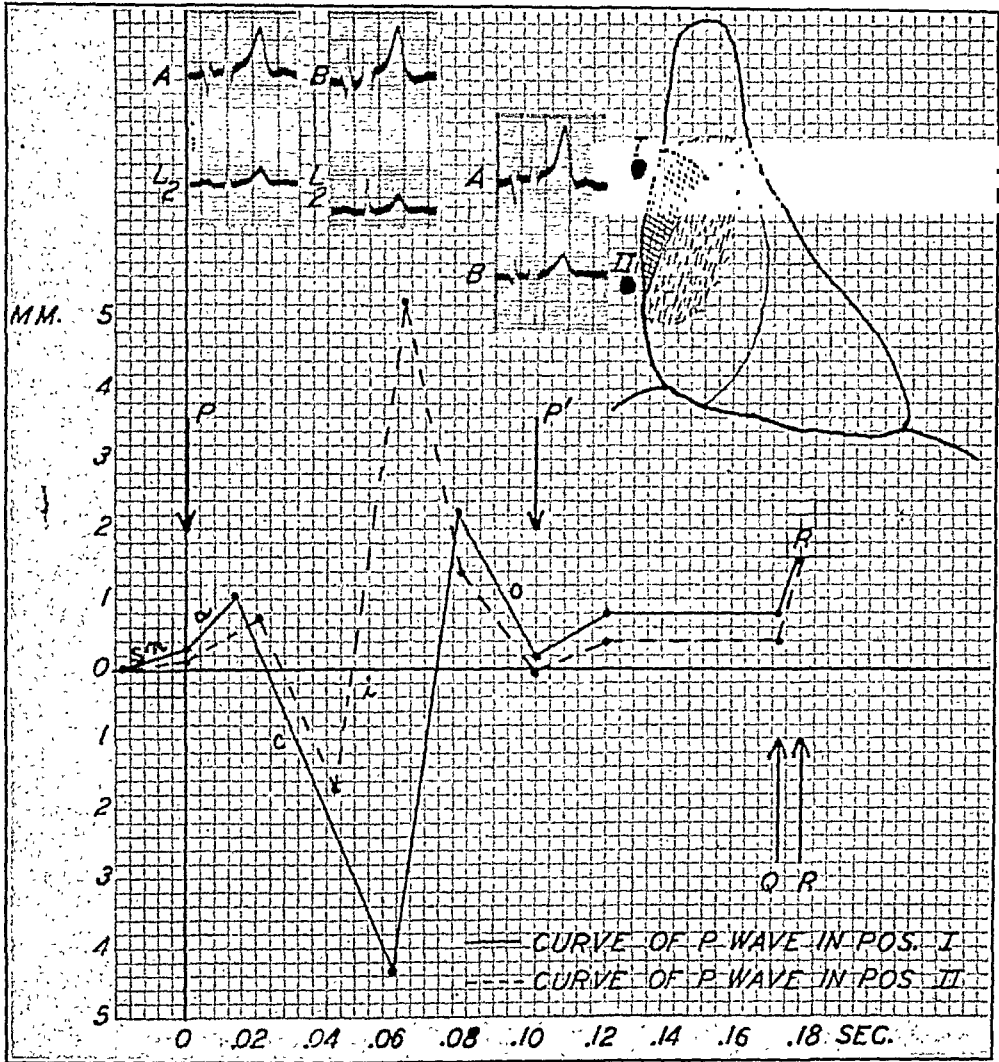


Fig. 5.—Simultaneous records from a normal subject aged fifty-two years, with graphs to illustrate the comparator findings. A double esophageal electrode was used. The arrows at *P* and *P'*, respectively, indicate the beginning and end of the P-wave in Lead II. For a full description see text.

change in the positions of the electrodes. The accompanying graphs are based on data obtained by careful comparator analysis of the auricular curves (Lucas comparator). The P-wave of Lead II is not drawn in full but is represented as beginning at the arrow *P* and end-

\*The subject was a man, aged fifty-two years, whose heart lay transversely on an unusually high diaphragm.

ing at the arrow  $P'$ . Each of the esophageal P-waves is shown plotted against that of Lead II and against one another.\*

An analysis of the graphs shows that in each a wave  $Sn$  representing a very small negative potential difference starts about 0.018 sec. before the onset of the P-wave in Lead II. This is followed by a larger sluggish upward or negative deflection  $a$ , and this in turn by a more sharply delineated downward or positive stroke  $e$ . Then occurs a rapid change to negativity and the sharp upstroke  $i$  is written. Finally a more leisurely deflection  $o$  seeks the isoelectric line and ends near it simultaneously with the end of the P-wave of Lead II (arrow at  $P'$ ).

*Discussion of Interpretation.*—The following explanation of these events is offered.

The low voltage wave  $Sn$ , which is not included in the P-wave of conventional Lead II, must represent the earliest electrical activity in the auricle. It may be that it is produced by the activation of the sino-auricular node. In this series it is frequently not discernible under the comparator for every position of the electrode, but when observed its duration is fairly constant. The range is from 0.011 to 0.018 sec., with an average of 0.0142 sec.

Wedd and Stroud<sup>61</sup> demonstrated in dogs with direct leads taken simultaneously with Lead II that the low grade electrical potential difference representing the activation of the sino-auricular node and the immediately adjacent structures were not included in the P-wave of conventional Lead II. They found that this wave usually started about 0.01 sec. before the onset of the P-wave. Eyster and Meek<sup>20</sup> confirmed this observation.

The wave which is designated  $a$  is thought to represent the summation of activation effects of parts of the auricle distant from the electrode. The alternative possibility that it may be due to interference from the indifferent electrode is not yet wholly to be excluded. To this end comparative records have been taken using Wilson's technic<sup>67</sup> for increasing the indifference of the remote electrode without significant diminution in the amplitude of the wave. The proposition that the wave  $a$  is wholly to be attributed to distortion from potential differences under the indifferent electrode is clearly untenable, for the occurrence of the  $Sn$  wave cannot be explained on this hypothesis.

The positive deflection  $e$  heralds the approach of the wave of excitation nearer and nearer to the cardiac tissue lying closest to the electrode. The work of Craib<sup>9</sup> indicates that this tissue, immediately before it becomes activated, is electropositive to the tissues which are undergoing activation in its immediate vicinity. If this interpretation

\*Corrections were made for differences in standardization in the esophageal curves to permit of accurate comparison.

is correct, then all of these effects (deflections  $S_n$ ,  $a$  and  $e$ ) are "extrinsic" by the definition of Lewis.<sup>32</sup> They are the effects produced by activation of more and less remote portions of the auricular myocardium.

The sudden change from positivity to negativity (at the junction of deflection  $e$  and  $i$ ) signals the arrival of the excitation wave at the cardiac tissue underlying the electrode. The negative deflection  $i$ , therefore, represents the phase of activation of this small region and is, consequently, "intrinsic" in character (Lewis<sup>32</sup>). In the language of Craib,<sup>9</sup> deflection  $i$  represents the passage of the activating train of doublets under the electrode; and the deflection  $o$  seeks the isoelectric line as the spread of excitation reaches the last unactivated portions of the auricle and dies away. The fact that deflection  $o$  seldom ends on the isoelectric line (but usually above or below it) and that the remainder of the P-R interval is likewise seldom truly isoelectric is in all likelihood due to the doublets of retreat or "repolarization."<sup>9, 68, 69</sup> This is a phase which will be more clearly demonstrated in a later consideration of the Ta-wave.

The graphical representation of curves  $A$  and  $B$  in Fig. 5 clearly indicates that the intrinsic deflections occur at different intervals in the P-wave, although their actual duration is fairly constant. The position of the  $i$  or intrinsic deflection in the auricular complex must, since it indicates activation of the tissue immediately underlying the electrode, be due to two factors. It must depend upon the distance separating that tissue from the origin of the wave of excitation (i.e., the length of the pathway traversed by the excitation wave) and upon the rate of conduction in the intervening auricular musculature. In the same way the position of the intrinsic deflection with respect to the isoelectric line (whether it starts below or ends above it) also depends on these factors. If the electrode becomes negative very late in the P-wave, the foregoing extrinsic effects are greater and the intrinsic deflection starts far below the isoelectric line; it may even end on it if the tissue over which the electrode lies is among the last of the parts to be activated.<sup>68, 69</sup> In these instances the occurrence of the  $i$  deflection may often be later than the summit of the P-wave in Lead II. The converse is also true. If it were possible to place the electrode exactly over the sino-auricular node, the intrinsic deflection would occur at the very beginning of P.<sup>38</sup> It would start from the isoelectric line and run above it. The extrinsic parts of the curve in this instance would be wholly written by the wave  $o$  (see Fig. 12, in which an extrasystole arose almost exactly under the electrode; also compare curve  $D$  with  $G$  in Fig. 4 B). Records obtained when the esophageal electrode is below the level of the lower pole of the auricle usually show a rather ill-defined or polyphasic P-wave of low ampli-

tude (*H*, Fig. 4 B). It is possible that such potential changes are in part due to electrical events occurring in the neighboring inferior vena cava.

The P-wave of conventional leads is thus to be regarded as the sum of numerous intrinsic electrical events of the type which has been described. This fact now demonstrated in the living human heart conforms with the experimental work of Boden and Neukirch<sup>6</sup> on the isolated human heart, of Wilson and others<sup>69</sup> on animals, as well as with the views expressed by Lewis.<sup>32</sup>

*Recapitulation of Section 2.*—When an electrode is placed in the human esophagus behind the left auricle, the recorded auricular complexes have a characteristic appearance so long as the electrode retains its close relations with the auricle. Such curves may be designated as “esophageal electrograms.” When the electrode is placed at a higher level, the recorded curves take on the character of indirect axial leads not unlike those of conventional Lead II. In auricular esophageal electrograms the outstanding features of the P-wave are its polyphasic form and the presence of an intrinsic deflection. The intrinsic deflections have been accepted, on the basis of evidence offered in Section 1, as accurate indications of the time of activation of the various auricular regions explored by the esophageal electrode. Analysis of the P-waves has further demonstrated that in some cases a small wave occurs before the onset of the P-wave of conventional Lead II. This has been attributed to the influence of electromotive changes incidental to the activation of the sino-auricular node.

### SECTION 3. OBSERVATIONS ON THE TA-WAVE AND AURICULAR EXTRASYSTOLES

That the P-wave of the standard electrocardiogram does not represent the electromotive changes of the auricle in their entirety has long been common knowledge. Although several observers (Kraus and Nicolai,<sup>28</sup> Samojloff,<sup>55</sup> Straub<sup>59</sup>) had previously described an “after-wave” which followed the P-wave of auricular contraction, Hering<sup>24</sup> was the first to prove that it was a part of the auricular complex. He named it the Ta-wave and considered it to be the auricular analogue of the T-wave of the ventricle. This work was confirmed in isolated heart preparations from various animals by the following workers: Hering,<sup>23</sup> 1909, frog; Eiger,<sup>13, 14</sup> 1911, 1913, frog; Noyons,<sup>46</sup> 1910-11, frog, carp; Samojloff,<sup>56</sup> 1910, cat; Kahn,<sup>25, 26</sup> 1909, 1911, dog; Mines,<sup>43</sup> 1912, frog; Bakker,<sup>3</sup> 1912, eel; Fredericq,<sup>22</sup> 1912, isolated strips of cardiac muscle of the dog; Nörr,<sup>45</sup> 1913, horse; Wiedemann,<sup>63</sup> 1917, dog; Rümke,<sup>54</sup> 1918, isolated strips of cardiac tissue from frogs; Boden and Neukirch,<sup>6</sup> 1918, and Boden,<sup>5</sup> 1921, the human heart.

A considerable range in duration of the Ta-wave was reported. Measured from the onset of P to the end of the Ta-wave (P + Ta interval) the following variations were noted: Eiger<sup>14</sup> (see curves 5, 6, 7, 11, 12, 12a of his paper) 0.25 to 0.8 sec.; Hering<sup>24</sup> (isolated frog's heart) 0.25 to 1.0 sec.; Eyster and Meek<sup>20</sup> (tortoise heart) 0.48 sec. (average); and Boden and Neukirch<sup>6</sup> isolated human heart 0.4 to 0.52 sec. No doubt the wide range found by the above authors was in part due to experimental conditions such as fatigue and temperature, but Boden<sup>5</sup> and Eyster and Meek<sup>20</sup> showed that other factors may change the P + Ta interval. The latter showed that in the tortoise vagal stimulation shortened the P + Ta interval and changed the form of the Ta-wave, and Boden<sup>5</sup> demonstrated a shortening of the P + Ta interval with acceleration of the heart rate. In a paper by Andrus and Padget,\* which has not yet been published, there is evidence that the P + Ta interval is shortened with shortening of the refractory period of the auricle.

Studies of the Ta-wave in the human subject in the past were confined to data obtained from conventional leads. Sprague and White<sup>58</sup> published observations on the Ta-wave in a series of thirty-seven patients with complete heart-block. In eighteen cases the wave was visible in one or more leads. These waves very seldom attained a height of 2 mm. and were opposite in direction to the P-wave. Caliper measurements of the curves showed a P + Ta interval ranging from 0.34 to 0.42 sec. (average 0.37 sec.). In other words the ratio  $\frac{\text{P + Ta interval}}{\text{Duration of P}}$  was about 3.7.

It has long been known that the myocardium of the ventricle bears a close relationship to the Q-T interval. It has also been a common observation that the auricular myocardium greatly exceeds the duration of the P-wave. An excellent illustration of this fact is shown in Fig. 8, p. 148 of the paper by Lewis, Feil and Stroud.<sup>37</sup> Caliper measurements of this figure show that the contractile phase of the auricle occupies 0.115 sec. and the total length of the myocardium 0.326 sec. This clearly shows that the auricular myocardium in the dog extends well into the ventricular complex under the conditions of normal rhythm.

That a parallelism exists between the auricular myocardium and the P + Ta interval is well shown in the monograph of Wenckebach and Winterberg<sup>62</sup> (Fig. 17, Tafel 9). The exact degree of correspondence between these values has been a subject of dispute<sup>10, 12, 42, 2</sup> but the interest in the Ta-wave largely arises from the relationship existing between the P + Ta interval (as indicating the total duration of the electrical events in the auricle), the auricular myocardium, and the length of the refractory period of auricular muscle.

\*Personal communication.

In the present series careful comparator studies were made of the P + Ta interval whenever opportunity presented. Several good examples of such waves were found. As would be expected, they were

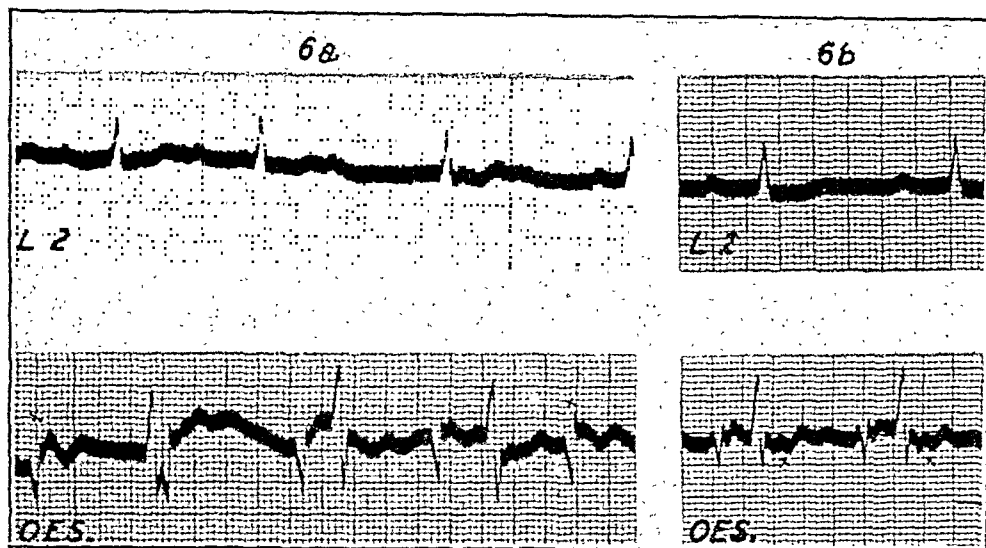


Fig. 6.—Patient B. M. The curves on the left (6a) show conventional Lead II (upper curve) and an example of an esophageal electrogram in a patient with complete auriculoventricular dissociation. The complexes marked with a cross are followed by Ta-waves. On the right (6b) are similar curves obtained with reduced string sensitivity from the same patient under conditions of first degree heart-block. The crosses indicate a small wave described in the text.

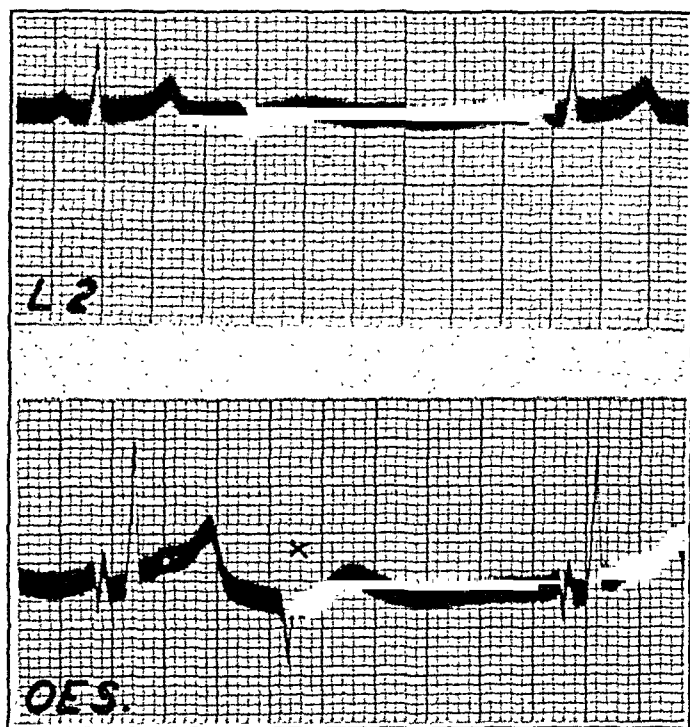


Fig. 7.—Patient B. C. Lead II above and an esophageal lead below. Complex marked by cross shows an ectopic auricular extrasystole followed by a Ta-wave. (See also Table I.)

of much greater amplitude and more clearly shown than in any previously published examples from the living human subject.

Figures 7 and 8 illustrate records from women in whom frequent auricular extrasystoles were occurring from ectopic foci. These are

not followed by ventricular contractions and the Ta-waves are clearly discernible both in the esophageal curves and in Lead II.

Figure 6 *a* shows records taken from a male subject forty-five years of age who suffered from Adams-Stokes attacks. A complete auriculo-ventricular dissociation is present (cf. also Fig. 9). At the points

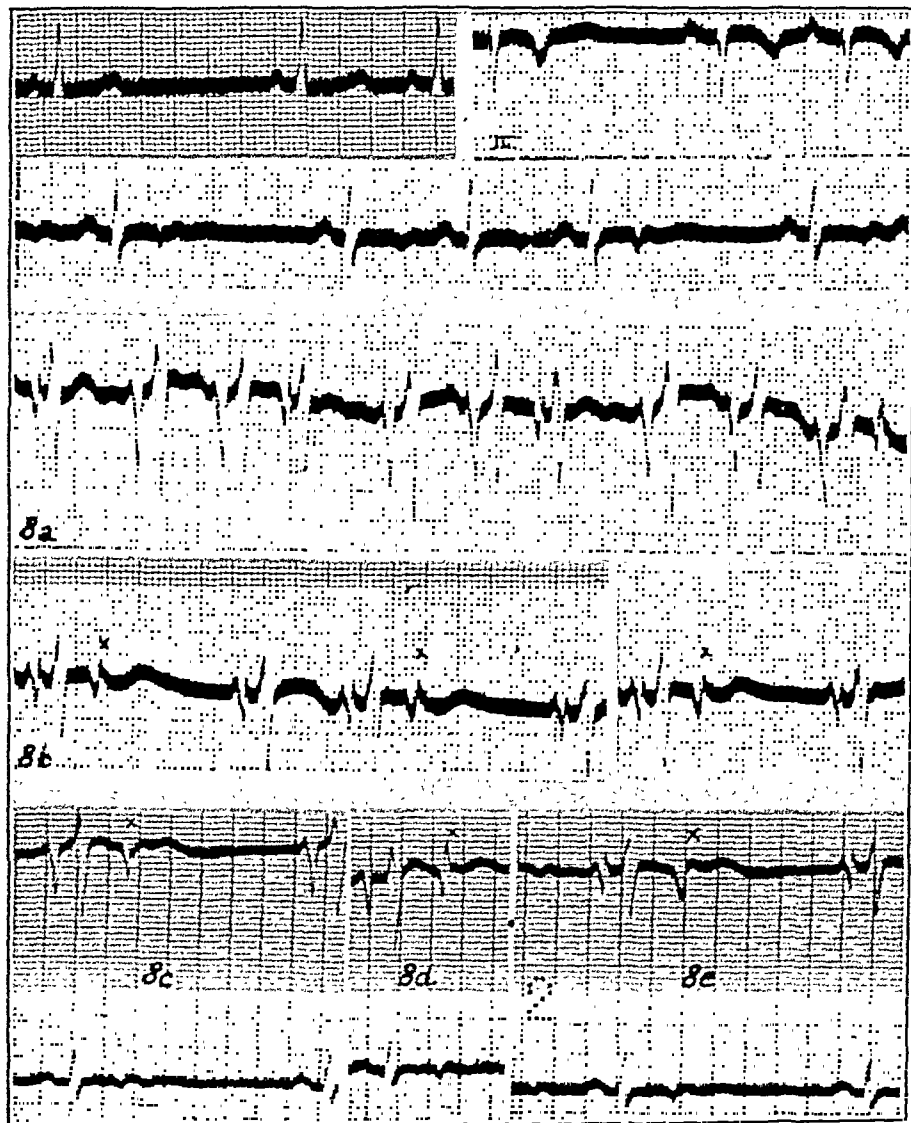


Fig. 8.—Patient A. J. (See Table I.) Records obtained from a patient showing numerous auricular extrasystoles. Conventional Leads I, III and II, are at the top. Records 8*a* and 8*b*, are esophageal curves from two different auricular sites. The crosses indicate auricular complexes followed by Ta-waves. Records 8*c*, 8*d*, and 8*e* show simultaneous records obtained one month later. Lead II is shown below, and curves from the esophageal electrode at various levels are shown above. Note the frequent occurrence of Ta-waves and the form of the ectopic P-waves as contrasted with those arising in the usual site.

marked with crosses the auricular complexes occur at the end of the T-wave of the preceding ventricular complex. Such P-waves are followed by a clearly defined biphasic wave, the Ta-wave. Figure 6 *b* shows records from the same man on the next day when sequential rhythm with a first degree heart-block was present. In the esophageal

records of this example a tiny wave interrupts the ventricular S-T interval. It is found, on measurement, that the distance from the beginning of the P-wave to the end of this wave is almost exactly equal to the P + Ta interval in Fig. 6 *a*. The record also suggests that, if a first degree heart-block were not present, this wave would fall near the onset or even on the ascending limb of the ventricular T-wave of esophageal electrograms. The comparator measurements obtained from the examples encountered in the series including those cited above are shown in Table I.

It will be seen from the measurements given in Table I, that the duration of the P + Ta interval as measured from the beginning of the P-wave to the end of the Ta-wave ranges from 0.405 to 0.503 sec. and that the ratio of  $\frac{P + Ta}{P}$  may be as high as 5.63 and as low as 4.05.

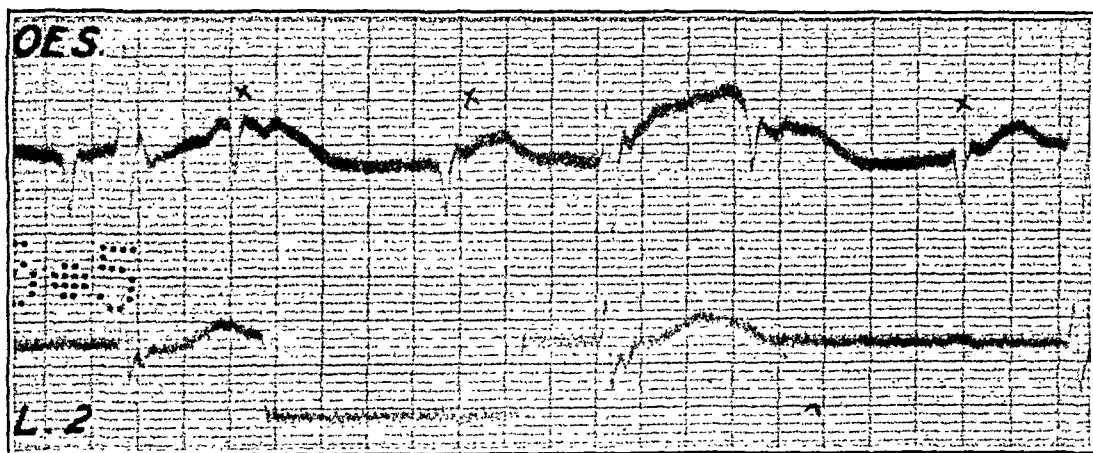


Fig. 9.—Patient H. G. Complete A-V dissociation. Upper curve, and esophageal lead. Lower curve, simultaneously written conventional Lead II. Complexes marked by a cross show Ta-waves. (See also Table I.)

The average ratio for all cases investigated is 4.72, a figure considerably greater than that found by Sprague and White.<sup>58</sup> This finding is of additional interest inasmuch as the duration of the P-wave as measured in esophageal electrograms is usually longer than that found in conventional leads (Fig. 5).

There is considerable variation in the character, though not the length, of the Ta-wave in the same patient, depending on the position of the esophageal electrode. The amplitude and the direction of the wave or its components are found to vary for different positions of the esophageal electrode. On occasions the after deflection is preceded by a return to the isoelectric line (Fig. 7) comparable to the S-T segment of the ventricle. In records from other esophageal sites in the same patient all trace of the isoelectric phase may disappear. Similarly a wave which is upright in one position of the esophageal lead may become biphasic in other positions. These variations are frequently to be seen affecting the P-R interval in many of the curves



TABLE I

PATIENT FIG. NO.	COMPLEX MEASURED	TYPE OF RHYTHM PRESENT	DURATION OF P-WAVE IN SECONDS	DURATION OF P + TR		AVERAGE P + TR P RATIO
				INTERVAL (TOTAL AURICULAR COMPLEX) IN SECONDS	RATIO P + TR P	
B. C. 7	Normal P-wave. The auricular extrasystole	Normal sinus rhythm with oc- casional auricular extra- systoles	0.0910 0.0974	0.480	4.94	4.94
B. M. 6 a.	Indicated by crosses	Complete A-V dissociation	0.0988 0.1001	0.5030 0.5006	5.19 5.00	5.095
B. M. 6 b.	Same patient. Indicated by crosses	Sinus rhythm with first degree heart-block	0.1029 0.1006	To end of small wave in S-T segment 0.5014 0.4930		4.87 4.90 4.885
A. J. 8	Indicated by crosses	Multiple auricular extra- systoles	0.1180 0.1146 0.1112	0.512 0.496 0.498	4.34 4.33 4.36	4.345
G. B.		Complete A-V dissociation	0.1064 0.1061	0.461 0.431	4.33 4.05	4.19
H. G. 9	Indicated by crosses	Complete A-V dissociation with auricular bigeminy	0.0712 0.0740 0.0728	0.408 0.406 0.405	5.49 5.49 5.63	5.53
B. S.		Complete A-V dissociation	0.1082 0.1074	0.440 0.438	4.06 4.08	4.07
A. A.		Complete A-V dissociation	0.1016 0.1008	0.462 0.457	4.55 4.58	4.57
Average Values			0.0992	0.464	4.72	

shown in this paper in which a high take-off of the Ta-wave causes a marked deviation of the P-R interval from the isoelectric line under conditions of sequential rhythm.

There is no doubt that the Ta-waves in esophageal curves exert some influence on the S-T segment of the ventricular curves for they certainly extend well into this part of the complex. This is well illustrated in Fig. 10. In this record there are three instances when the ventricular complex is not preceded by an auricular complex (sino-auricular block or standstill). The S-T segments of these ventricular curves are decidedly different from those modified by an antecedent auricular complex. The form of the ventricular complexes themselves does not vary, and it is justifiable to assume that they are all of supra-ventricular origin. It is too much to suggest that comparatively large

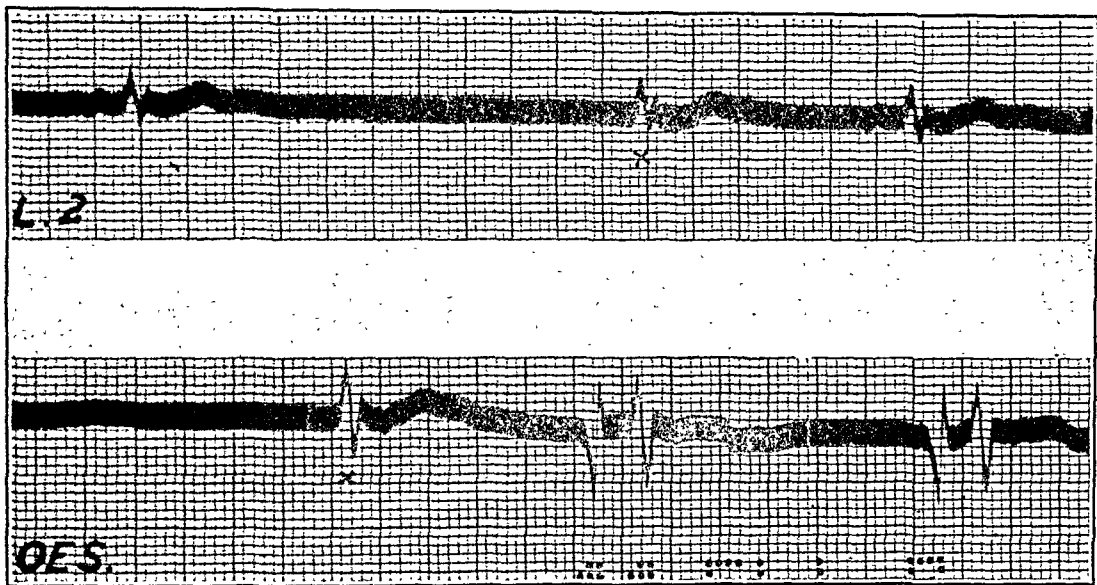


Fig. 10.—Patient W. E. Conventional Lead II above, esophageal electrogram below illustrating sino-auricular block and the modifying effect on the S-T segment by the Ta-wave. Complexes marked with a cross denote ventricular escape.

modifications of the ventricular S-T segment may be due to this cause in indirect or conventional leads. It should be noted, however, that there is great variation in the amplitude of auricular T-waves from patient to patient and that Sprague and White<sup>58</sup> have been able to detect definite waves in 50 per cent of their series, some being as high as 2 mm. In view of these facts it is timely to sound a warning against interpreting minor deviations of the S-T segment of conventional curves as evidence of ventricular damage, for they may be caused by auricular events which extend farther into the ventricular complex than has generally been recognized.

*Auricular Extrasystoles.*—Early papers by Lewis<sup>33, 35</sup> have placed emphasis on the variations in form of the P-waves of conventional leads as indicating the ectopic origin of auricular extrasystoles. In Figs. 7 and 8, which have been referred to before, the differences in the

form of the P-wave of the esophageal electrograms in extrasystolic and normally occurring complexes are well illustrated. In Fig. 11 an example is given of auricular extrasystoles occurring in the presence of complete A-V dissociation, the interpolated beats causing an auricular bigeminy. The differences in the form of the coupled auricular beats in these records recall the P complexes of Fig. 5. In Fig. 5

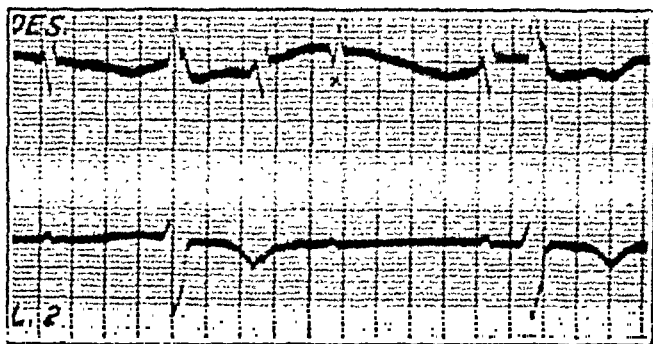


Fig. 11.—Patient G. B. A case of complete A-V dissociation and intraventricular block which illustrates auricular bigeminy at points indicated by crosses. The interpolated auricular complexes clearly arise from ectopic foci since they differ in form from the regularly occurring beats.

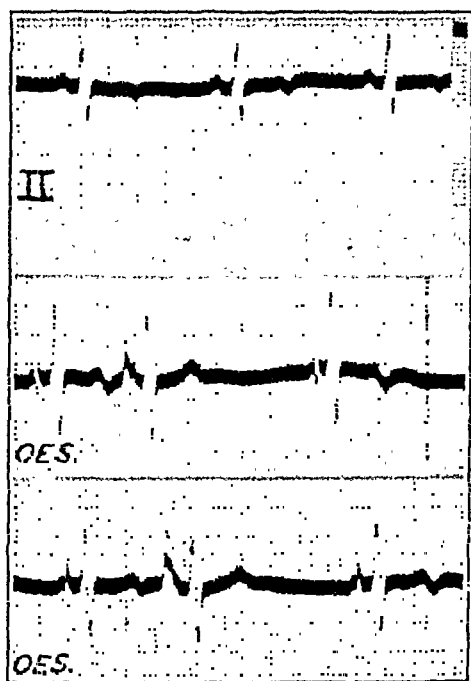


Fig. 12.—Patient D. W. Auricular extrasystoles. The lower two records are taken from esophageal leads. Lead II is shown above. The extrasystoles are indicated by crosses. The ectopic complex in the lower record arises from the region almost exactly below the electrode. Standardization, 1 mv. = 7 mm. in esophageal curves.

one focus is acting as origin for all auricular beats, and the differences in the complexes obtained from the two separate exploring electrodes are due to the fact that the electrodes were at unequal distances from the sinus node. Figure 11 presents the converse of this, for here the single electrode remained stationary, and two different foci were in effective action.

In Section 2, reference has been made to a record showing an extrasystole originating almost exactly under the esophageal electrode. This is exemplified in Fig. 12 (lower curve). The complex begins at once with an intrinsic deflection, and this is followed by a long extrinsic after effect. The total duration of the ectopic P-wave is 0.1367 sec. as compared with 0.0849 sec. for the normally occurring P-waves. The following explanation for this prolongation of the length of the P-wave appears reasonable. It is known from the experiments carried out in Lewis' laboratory<sup>34, 39, 38</sup> that the normal excitation wave starts from the sino-auricular node and spreads radially throughout the auricle. In the present instance the wave is known to arise at an eccentric point in the left auricle at some distance from the sinus node. To reach the furthestmost tissue of the right auricle, it must therefore travel considerably farther and consume more time in transit than is normally the case.

It seems safe to predict that a more general use of the esophageal lead might soon result in criteria for the localization of auricular extrasystoles and thus supplement the early work of Lewis<sup>35</sup> in this field.

*Recapitulation of Section 3.*—Several examples of clearly visualized auricular T-waves have been illustrated, measured, and discussed. The conclusion has been reached that this part of the auricular electrical cycle may extend much farther into the S-T segment of the ventricular complex than has hitherto been recognized and cause minor deviations from the isoelectric line in conventional leads.

Examples of auricular extrasystoles have been illustrated and the suggestion has been made that a wider use of the esophageal method might be helpful in determining the position of the focus responsible for the ectopic beats.

#### SECTION 4. AN ANALYSIS OF THE VENTRICULAR COMPLEXES OF ESOPHAGEAL LEADS IN NORMAL INDIVIDUALS

In Fig. 4 B, in which the standardization of the string is the same in all curves including the conventional and chest leads, it is at once apparent that the whole of the ventricular complex is exaggerated when compared with Lead II. The T-wave is wider and more pointed, having its onset earlier and frequently being followed by a U-wave.

It is further to be noted that in no curve obtained with the esophageal leads in Figs. 4 B, and 5, is a Q-wave present. Comparison with Lead II in this latter figure shows that the onset of the R-wave in the esophageal lead precedes that in Lead II. Under the comparator (as is indicated in the graph) the R-wave of the esophageal curves is seen to coincide with the earliest sign of activity in Lead II. In the conventional lead this event is written as a tiny Q-wave. In all of the normal controls and in all but a very few of the abnormal cases the

earliest sign of ventricular electrical activity is always an upstroke or R-wave when the electrode is behind auricular tissue. The onset of the R-wave in such esophageal curves coincides with R of Lead II only when no trace of a Q-wave is present in that lead.

The following suggestion is offered in explanation of this fact. If an exploring electrode is placed against, or almost against, auricular musculature, then at the onset of ventricular excitation it is tapping the electropotential changes occurring in the ventricle under peculiar circumstances. It is connected to the internal surface of the ventricle by an electrolytic medium: the wall of the auricle and the auricular contents. The atrioventricular valves are open. Now it has repeatedly been shown that the earliest sign of activity in the normally beating ventricle is manifested by electronegativity of the endocardial surface. Lewis<sup>40</sup> and Wilson<sup>68</sup> have both shown, in collaboration with others, that this electrical change can be detected by an electrode placed in the blood inside the ventricular chamber. By analogy the esophageal electrode, though more remotely situated, registers initial negativity as the first sign of ventricular activity.

Apart from the above mentioned peculiarities, *the ventricular complexes obtained when the esophageal electrode is lying close to auricular musculature* closely simulated in their general character the QRS complexes of Lead II. Although this was true in all but one subject of the control series, there were frequent exceptions in the series as a whole. In such instances the ventricular complexes of the esophageal curves had a biphasic form with a well-defined S-wave. An analysis of the material of the entire series to determine the association of such biphasic esophageal complexes to ventricular preponderance gave the following results: In all cases of right ventricular preponderance the esophageal ventricular complexes were always monophasic and upright, and in all cases of left ventricular preponderance they were biphasic with deep S-waves. In the cases which fell between these two extremes, there was in general a close similarity to the QRS complexes of Lead II. In those instances in which the QRS complex of Lead II was monophasic while some of the esophageal ventricular complexes were biphasic, the position of the electrical axis in conventional leads approached in greater or less degree the border line between the normal range and left axis deviation. In these circumstances the biphasic ventricular complexes occurred in the curves obtained from the lower auricular positions of the esophageal electrode (Figs. 5 and 13). In other words, the ventricular curves showed an increased depth of the S-wave as the electrode approached the atrioventricular groove and the ventricular musculature.

*When the electrode is placed below the level of the auricular musculature and close to the basal portion of the left ventricle* (position H, Fig. 4 A), characteristic changes occur in the form of the electro-

gram. The P-waves take on the slurred ill-defined form which has already been noticed in Section 2, while the QRS complexes at once become decidedly biphasic in character, a diminished R-wave being followed by an exaggerated, deep S-wave (Fig. 13). This striking alteration in the form of the ventricular complex for juxta-ventricular positions of the esophageal electrode in normal individuals demands elucidation. Most particularly is it desirable to determine whether the appearance of the S-wave is due to the influence of an intrinsic deflection arising in the ventricular area explored.

Admittedly, an electrode in the lower esophagus does not always lie as close to the heart as it does at the auricular levels (Fig. 1), but there can be no doubt that it is, in this location, closer to the base of the left ventricle than is a precordial lead to the surface of the right ventricle. It follows, therefore, that the arguments of Wilson and his associates<sup>68</sup> relating to intrinsic deflections in precordial leads over the right ventricle must apply *a fortiori* to the esophageal electrode when the latter is employed as an exploring lead to the left ventricle.

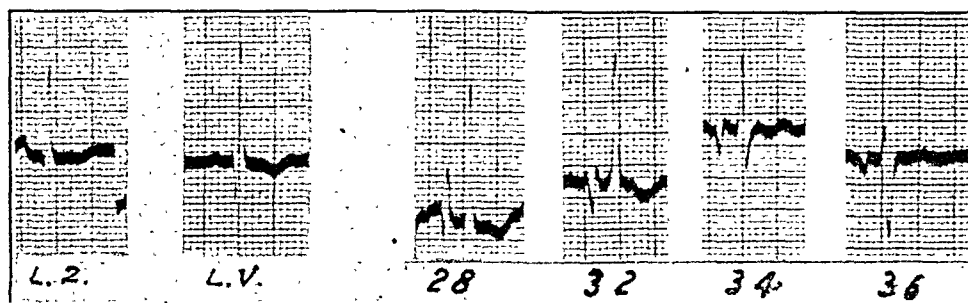


Fig. 13.—Patient L. B. Single records demonstrating the changes in the ventricular complex in esophageal electrograms for different positions of the electrode. Lead II and chest Lead V are included for comparison. The figures below the records indicate the depth of the electrode in centimeters as measured from the teeth. Note the appearance of an S-wave in the QRS complex when the electrode is near the atrioventricular groove (at 34 cm.) and the diminution of the R-wave and great increase in the amplitude of S when (at 36 cm.) the electrode reaches a juxta-ventricular position.

Lewis<sup>32</sup> (p. 115) has estimated on the basis of experimental findings in dogs that, in a normal human subject, the basal portion of the left ventricle may be activated as late as 0.065 sec. after the beginning of ventricular excitation. In arguing from this standpoint, it becomes obvious that a ventricular intrinsic deflection recorded by the esophageal lead must occur relatively late and, in fact, almost at the end of the QRS complex. As Lewis and Rothschild<sup>40</sup> have shown, the excitation wave spreads very rapidly along the Purkinje system of both ventricles, the septal portions of the musculature being first excited. The main factor responsible for the difference in time at which signs of activation appear on the epicardial surfaces of the ventricles is the relative thickness of the slowly conducting ventricular musculature of the two chambers. These facts explain why, in the normally functioning heart, the pericardial surface of the right ventricular base is

activated in advance of the corresponding portion of the left ventricle. This also explains why right ventricular preponderance tends to reverse this relationship and why preponderance of the left ventricle tends to accentuate the differences in time of activation.

It is the rule in all the normal cases studied by the esophageal electrode in juxta-ventricular positions to find that the beginning of the upstroke of the S-wave occurs progressively later as the electrode is moved upward and nearer to the free margin of the ventricular base. In the series of fifteen normal subjects the average time of onset of the upstroke in the S-wave has been found to lie between 0.04 and 0.058 sec. after the beginning of ventricular activity. In cases of left ventricular preponderance it has occurred as late as 0.063 sec. and its time of occurrence has shown an approximate relationship to the total length of the QRS complex. When marked right ventricular preponderance is present S is sometimes absent and may be represented by a notching or slurring in the downstroke of the R-wave. Because almost all esophageal records from the left ventricle of normal cases show a well-defined R-wave, it is extremely unlikely that the onset of the S-wave in the electrograms is to be taken as the exact time of onset of the intrinsic deflection arising in the muscle underlying the electrode. In other words the R-wave of such esophageal electrograms is certainly extrinsic in nature and is produced by the activation of areas of ventricular muscle at some distance from the electrode. The downstroke of the R-wave must represent the development of electropositivity in the small area tapped by the electrode. It is the resultant of extrinsic potential variations produced at a distance and charges produced in the area immediately adjacent to the electrode. The nearer the electrode is brought to the surface of the ventricle, the less is the manifest influence of the distantly arising extrinsic potential differences, and the less the influence of potential changes at the remote electrode on the left leg. For this reason curves obtained with the electrode closely opposed to the ventricle have the smallest R-waves and the largest S-waves and are those in which a determination of the time relationships of the upstroke of the S-wave most accurately represent the true position of the intrinsic deflection arising from the base of the left ventricle.

An experiment was devised to prove that the above argument is substantially valid and that the intrinsic deflection from the epicardial surface of the base of the left ventricle occurs at the approximate time occupied by the upstroke of the S-wave in esophageal leads from that part of the heart.

A dog weighing 12 kg. was anesthetized with dial and urethane. The heart was exposed by the removal of a section of the thoracic cage and splitting of the pericardium. The free end of a woolen strand was stitched to the left ventricle 1.5 cm. from the atrioventricular groove. The remainder of the strand was insulated

by rubber so that it was prevented from coming into contact with any part of the heart. The strand of wool, thoroughly moistened in saline, was fixed in a "non-polarizable" kaolin-paste copper-sulphate electrode, which in turn was attached to the right arm terminal of a two-stringed Cambridge galvanometer. The free ends of the thread stitching the electrode to the heart were then passed through the pericardium and loosely tied around the underlying esophagus at a point opposite the site of fixation. An esophageal electrode of the type used in clinical research was passed into the esophagus until the silver bulb lay opposite the ventricular area tapped by the direct lead. This electrode was attached to the right arm terminal of the second galvanometer string. Indirect Lead II was attached to a Hindle galvanometer. The left leg was used as a site for electrodes, completing each of the

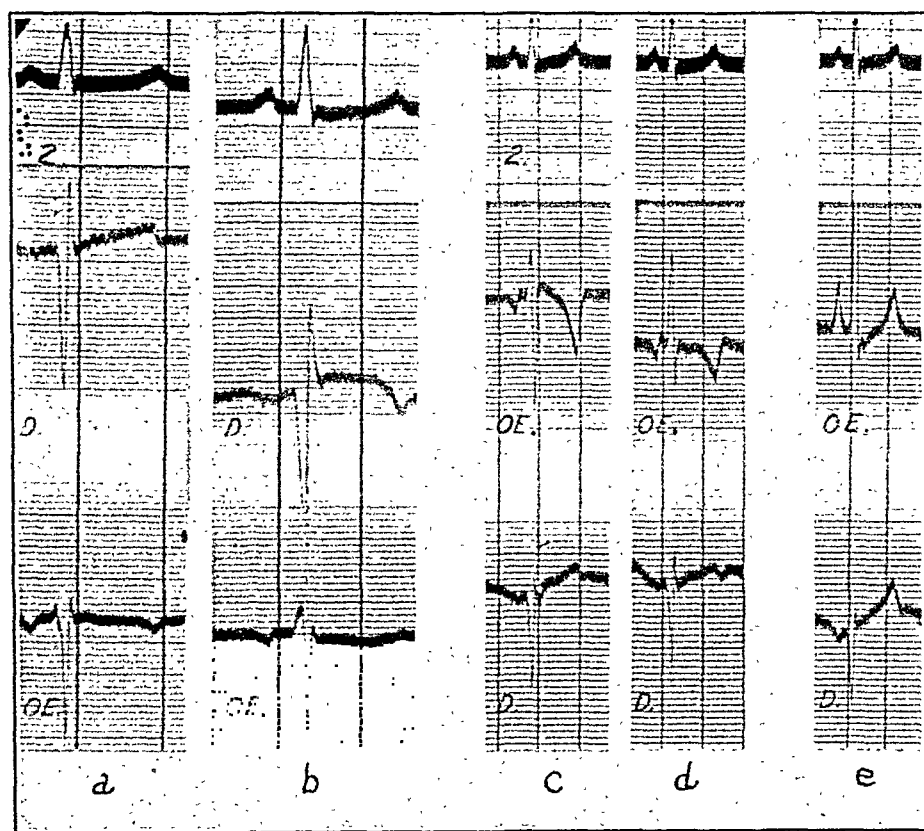


Fig. 14.—Records illustrating the findings in three animal experiments to determine the relationship existing between the S-waves of juxta-ventricular esophageal electrograms and the true intrinsic deflections as obtained by direct leads from the base of the left ventricle. The leads are recorded simultaneously; 2, Lead II; OE, esophageal curves; and D, direct leads. For a full description see text.

three circuits. The resistances of all three circuits were balanced. By the use of appropriate prisms simultaneous tracings from the three leads were recorded on one camera.

Sample curves from three of five such experiments are shown in Fig. 14. Records *a* and *b* are taken from two different dogs. Although no R-wave is present in either of the direct electrograms (middle curves), the (lower) curves from the semidirect leads have an initial upward deflection. The onsets of the upstrokes of the S-waves are also later than the onsets of the simultaneously recorded intrinsic deflections in the direct leads, but they coincide exactly with the point at which the latter cross the isoelectric line.



Records *c*, *d*, and *e* of Fig. 14 have been obtained from a third animal. The esophageal leads in this instance are recorded in the middle and the direct leads in the lower curves. Record *c* is very similar to records *a* and *b*, but in record *d* the esophageal electrode has been displaced to a position 2 cm. away from the heart, while in record *e* the electrode has been moved to a position 2 cm. nearer the head of the animal. Both of these maneuvers have resulted in noteworthy alterations in the QRS complexes of the curves recorded by the semidirect (esophageal) lead. The R-waves in each instance have become much more prominent, and the S-waves are greatly reduced in amplitude. The upstroke of the S-wave in records *d* and *e* has also lost all pretense of representing the position of the intrinsic deflection signalling the time of activation of the base of the left ventricle. The results of these and two other similar experiments are important because they afford proof that the intrinsic deflections from the base of the left ventricle normally occur near the end of the QRS complex and that the deep S-wave of juxta-ventricular esophageal electrograms is to be attributed to the influence of such intrinsic deflections.\* It is concluded that in the normally beating human heart the upstrokes of the S-waves of esophageal electrograms from the region marked *H* in Fig. 4 A, Section 2, are indicative of the approximate time at which the adjacent ventricular surface becomes activated as long as the electrode is fairly close to the ventricle. A review of the findings in fifteen normal cases indicates that abnormal delay in activation of the base of the left ventricle is demonstrated when the upstroke of a deep S-wave of a juxta-ventricular esophageal electrogram begins later than 0.065 sec. after the onset of ventricular activity. In cases of intraventricular delay it is likely that the esophageal electrogram is usually a more faithful guide to the time of activation of the left ventricular base, for, under the circumstances, there may be less interference from powerful extrinsic electrical forces arising in remote areas of the heart, these having had time to pass the zenith of their influence.

*Recapitulation of Section 4.*—When the esophageal electrode is lying behind auricular musculature the ventricular complexes, though somewhat exaggerated in amplitude, commonly bear a close resemblance to those of conventional Lead II. In cases of left ventricular preponderance they are usually biphasic in type, particularly when the electrode approaches the auriculoventricular junction. When the electrode is placed below the auricle in a juxta-ventricular position, not only do the P-waves become ill defined but, in the absence of marked right ventricular preponderance, the QRS complexes invariably become ex-

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\*The interference from extrinsic sources invariably acts to delay the onset of the upstroke of S. For this reason the onset of the true intrinsic deflection tends to precede this upstroke. It is probable, therefore, that in a normal human heart the base of the left ventricle is never activated later than 0.055 sec. after the beginning of the QRS complex.

aggeratedly biphasic. The amplitude of R decreases and S becomes disproportionately large. From both theoretical and experimental standpoints there is strong evidence that, provided the electrode is close to the base of the ventricle, the upstroke of the S-wave may be accepted as indicating the approximate position of the intrinsic deflection caused by the activation of the region adjacent to the electrode. The region so tapped by the esophageal electrode in its juxta-ventricular position is the base of the left ventricle, and the position of upstroke of the S-wave of such curves may therefore warrantably be taken as a guide to the time at which the pericardial surface of that part of the heart becomes activated. Abnormal delay in activation of the base of the left ventricle is certainly indicated when in such curves a deep S-wave begins its upward stroke later than 0.065 sec. after the onset of the QRS complex.

#### SECTION 5. OBSERVATIONS ON CLINICAL CASES OF BUNDLE-BRANCH BLOCK AND VENTRICULAR EXTRASYSTOLES

*Bundle-Branch Block.*—The literature bearing on this much disputed subject has recently been reviewed by Mahaim.<sup>41</sup> It is sufficient for immediate purposes to indicate the present views of the opposing schools of opinion. The "old terminology," so widely accepted on the evidence offered by Kraus and Nicolai,<sup>29</sup> Eppinger and Rothberger,<sup>17</sup> Eppinger and Stoerk,<sup>18</sup> Lewis,<sup>36</sup> and Carter<sup>7, 8</sup> (to mention only a few), has confidently survived the early criticisms of Fahr,<sup>21</sup> and Oppenheimer and Pardee<sup>47</sup> only to bend before renewed and recent attacks. The startling results of Barker, Macleod, Alexander, and Wilson<sup>4</sup> from experiments on the exposed living human heart in situ have been followed by painstaking and original researches by Wilson, Macleod and Barker.<sup>64, 68, 70, 71</sup> The results of their investigations have led them to conclude that the interpretations of the "old terminology" are precisely the reverse of what they should be. The evidence offered in support of the "new" and now widely accepted interpretation of standard records in cases of bundle-branch block has in turn been called in question by Rothberger<sup>50</sup> and Mahaim.<sup>41</sup>

Wilson and his collaborators<sup>68</sup> postulate that curves showing divergence of the chief deflections in standard Leads I and III indicate left bundle-branch block; whereas these, by far the commonest type found in intraventricular delay in clinical electrocardiography, have previously been attributed to block of the right bundle. A considerable part of the evidence which has been brought in support of their conclusions is electrophysical and mathematical in character, but the data have been used as a foundation for careful research on animals and clinical cases. The approach of the Wilson school has been essentially on a functional basis in that they have largely disregarded morbid anatomical investigations and have used the electrocardiograph as an

indicator for determining the order in which the ventricles become activated. To this end they have employed precordial leads in an exploring rôle and have attempted by this means to detect delay in the activation of the affected ventricle by measuring the time of occurrence of the intrinsic deflections from both chambers. In their investigations they have had to contend with certain difficulties, not the least of which has had to do with the effective application of the exploring electrode. It is, apparently, comparatively easy to obtain trustworthy intrinsic deflections from the right ventricle by chest leads, but Wilson<sup>68</sup> has himself expressed dissatisfaction with some of his attempts to "tap" the left ventricle.

Rothberger<sup>50</sup> and Mahaim,<sup>41</sup> in company with a considerable number of other workers, are ranged in opposition to the views of the Wilson school and the new terminology. Both of these observers believe that the right bundle is much more commonly blocked than the left but that an interruption of conduction in the right bundle is very seldom unassociated with a partial block on the left side. Rothberger bases his conclusions on earlier experimental work with Winterberg<sup>52, 53</sup> which he has recently elaborated.<sup>50</sup> Mahaim<sup>41</sup> has attacked the problem by meticulous researches in the pathological field. He has subjected the whole of the previously published evidence to a strict analysis and has added much new material from his own exhaustive microscopic studies of post-mortem hearts from clinical cases of intraventricular block. While it may be stated that the majority of the electrocardiographic curves from his cases are not typical examples of the classical types described by Carter,<sup>7, 8</sup> a great contribution has been made by Mahaim in pointing out the comparative rarity of lesions confined to a single bundle in either ventricle. Mahaim believes that the great majority of cases of bundle-branch block are due to coronary arterial disease. He is particularly insistent that the commonest syndrome is due to a total block of the right bundle associated with block of the anterior branches of the left bundle. As an occlusive process in the anterior interventricular or septal branch of the anterior descending branch of the left coronary artery is alleged to interfere with the blood supply to these parts of the ventricular conducting system, there is cogency in his argument, and the concept of "mixed blocks" is rapidly gaining wider acceptance.<sup>50, 52, 53, 65, 66</sup>

As soon as it became evident that the lower esophageal lead offered an approach to the base of the left ventricle, the method was applied to the problem in hand. Fourteen cases of bundle-branch block were investigated along the following lines. The esophageal electrode was placed with the aid of fluoroscopy in a position close to the basal surface of the left ventricle (Position *H*, Fig. 4 A) below the level of the left auricle. A small German silver electrode was placed on the chest at a point 3 cm. to the left of the sternum in the fourth

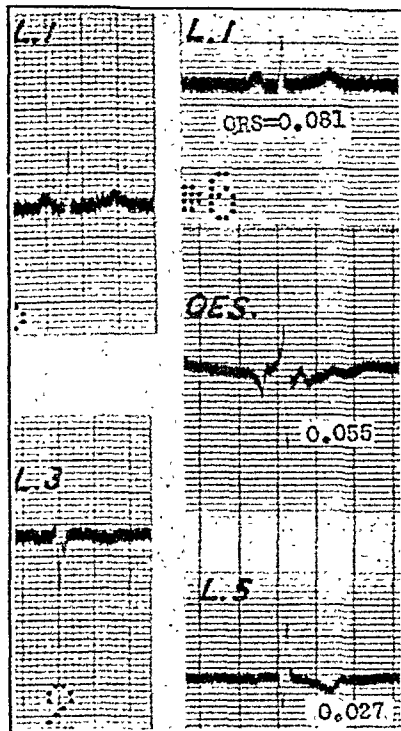


Fig. 15.—Patient G. G. From a man aged forty-eight years who showed no sign of intraventricular block. Standard Leads I and III are indicated on the left. A triple record illustrates the simultaneous recording of Lead I above, juxta-ventricular esophageal lead in the middle and Lead V below. The times of onset of the intrinsic waves in the two exploring leads are indicated by decimal fractions of a second. This example serves as a normal control for comparison with the curves of bundle-branch block.

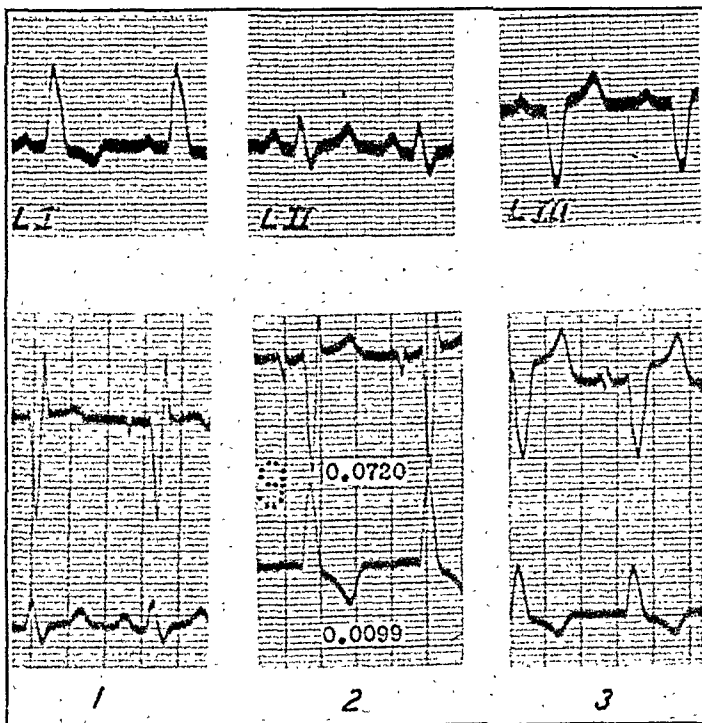


Fig. 16.—Patient M. H. Bundle-branch block of common type. Upper row: Leads I, II, and III. Lower row: 1, esophageal electrode at 40 cm. combined with Lead II; 2, esophageal electrode at 38 cm. combined with chest Lead V; 3, esophageal electrode at 36 cm. combined with Lead II. The numbers below the curves in record 2 denote the time at which the respective intrinsic deflection begins.

Conclusion: An example of left bundle-branch block.

interspace. The right arm terminal of one string of a two-stringed Cambridge galvanometer was attached to each of these exploring electrodes and left leg terminals to remote or indifferent electrodes on the left leg. *Electronegativity of both the esophageal and precordial exploring electrodes under these circumstances was indicated in the curves by sharply delineated upward deflections.* The times of occurrence of such major upwardly directed deflections were determined by the comparator by measuring from the earliest sign of ventricular activity to the onset of the said deflections.

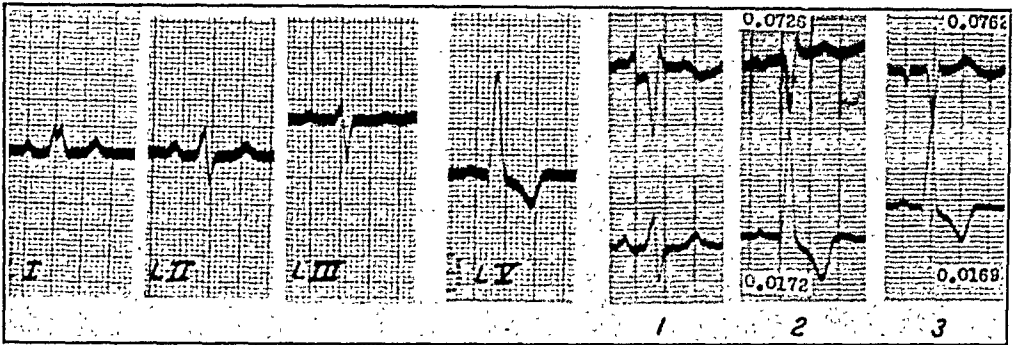


Fig. 17.—Patient A. O'L. Bundle-branch block of the common type. From left to right the single curves are Leads I, II, and III; chest Lead V. From left to right double curves (esophageal curves above): 1, esophageal electrode at 36 cm. combined with Lead II; 2, esophageal electrode at 36 cm. combined with chest Lead V; 3, esophageal electrode at 34 cm. combined with chest Lead V.

The decimal fractions refer to the onset of the intrinsic deflections in the respective curves. Standardization of the esophageal fractions is illustrated in record 1.

Conclusion: Left bundle-branch block.

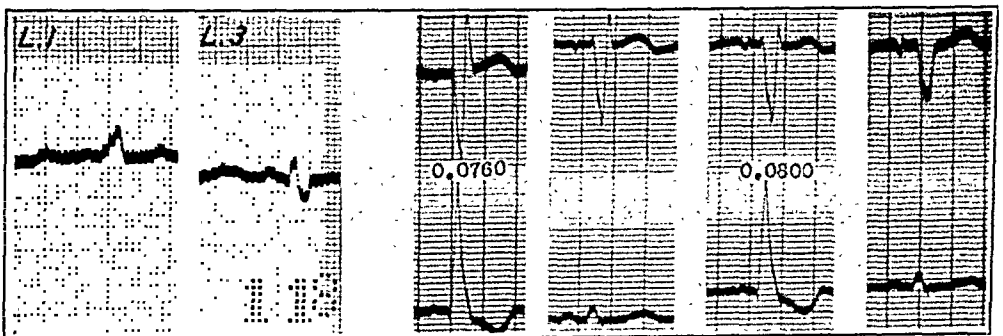


Fig. 18.—Patient E. W. Bundle-branch block of the common type though of low voltage. Single curves Leads I and III. In the double records the upper curves are from the esophageal electrode at 42, 40, 38.5, and 37 cm. depths, respectively, from left to right. Chest leads and Lead II are shown below. The numbers refer to times of onset of the intrinsic deflections in decimal fractions of a second in the esophageal curves.

Conclusion: Lag of the left ventricular base.

In the illustrations the times of onset of the chief upwardly directed deflections, signalling activation of the respectively adjacent muscle areas, have been indicated by decimal fractions of a second. These measurements have been placed below and near the beginning of the significant upward deflections in every instance. Figure 15 illustrates a typical result of applying the above procedure to a patient who showed no electrocardiographic sign of intraventricular block. The

accompanying Figs. 16 to 22, inclusive, demonstrate some of the results obtained by using this method in cases of intraventricular delay. Comments on detail are included in the legends to the illustrations.

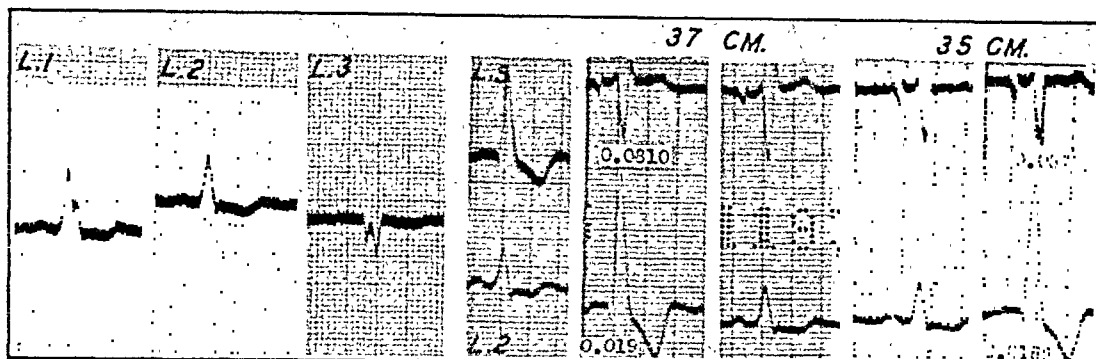


Fig. 19.—Patient M. G. Bundle-branch block of the common type. From left to right, single curves, Leads I, II, and III. From left to right, double curves, chest Lead V above and Lead II below. In the remaining curves the esophageal curves are the upper ones paired in turn with the chest lead, and Lead II at the depths of 37 and 35 cm. The numbers in fractions of a second indicate time of onset of the intrinsic deflections in the respective leads.

Conclusion: Left bundle-branch block.

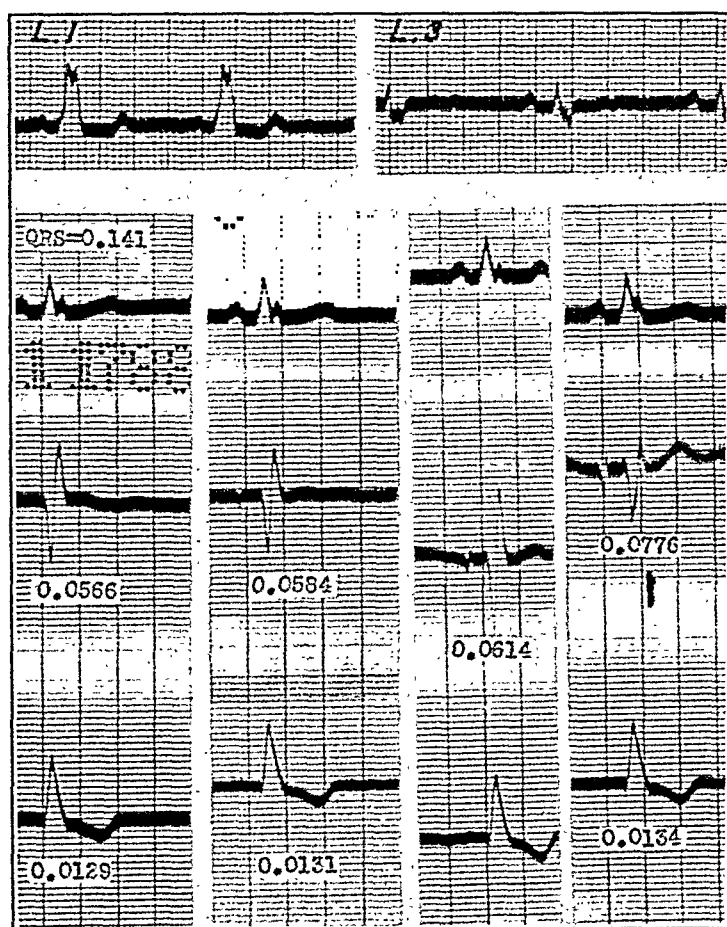


Fig. 20.—Patient H. I. Single records: Leads I and III. Triple records: Lead II above, esophageal curves in the middle, chest lead below. Numbers refer to onsets of the respective intrinsic deflections. The standardization of the exploring leads has been reduced to 1 mv. = 5 mm.

Conclusion: No lag of the left base. This is probably a bundle-branch block involving some part of the left ventricle other than the base.

The view is not entertained that the chief upward deflections in either the precordial or the esophageal tracings are exactly compar-

able in their time relations to the true intrinsic deflections as obtained by direct leads. The term "intrinsic deflection" is nevertheless used hereafter to describe the main upward strokes in semidirect curves since it has been proved by Wilson and his collaborators<sup>68</sup> and by experiments which have already been described (Fig. 14) that these indicate the approximate times of activation of the respectively explored areas. The esophageal lead is indeed only a modification of the approach of Wilson and his colleagues, but it is believed that the method offers a much more trustworthy guide to the intrinsic elec-

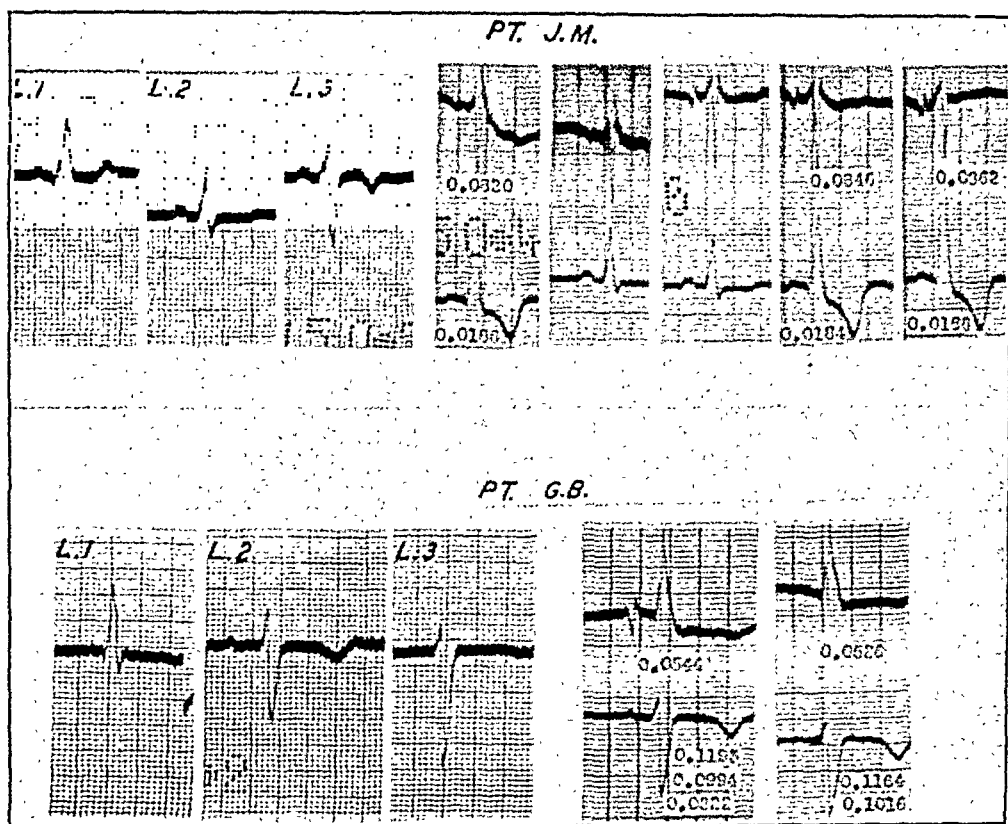


Fig. 21.—Patient J. M. From left to right single curves are Leads I, II, and III. Double curves, left to right: esophageal electrograms above at the depths 40, 40, 38, 38 and 36 cm., respectively, from the teeth, and below chest and conventional Lead II recorded simultaneously with the esophageal curves. The numbers denote the times of onset of the intrinsic deflections in esophageal and chest leads.

Conclusion: An example of left bundle-branch block.

Patient G. B. Left to right, single curves Leads I, II, and III and two examples of juxta-ventricular esophageal electrograms (above) recorded simultaneously with the precordial lead over the right ventricle. The numbers denote time of onset of intrinsic deflections in fractions of a second. Those pertaining to the right ventricle are placed opposite slurred components of the intrinsic deflection. The case is clearly one of right ventricular block. See text for discussion.

trical events in the basal portions of the left ventricle than can be obtained by chest leads. The view is held that the simultaneous use of both leads permits reliable conclusions to be drawn as to the order of activation of the ventricular areas underlying the electrodes.

In ten of the fourteen cases of bundle-branch block investigated by double semidirect leads unmistakable evidence was obtained of de-

layed activation of the left ventricle in the presence of early activation of the right. In two cases (see Fig. 20) there appeared to be no noteworthy lag in either of the explored areas although the QRS complexes as a whole were of abnormally long duration. The conclusion was reached that the interruption of conductivity in these cases must have affected some unexplored part of the ventricles, possibly in the anterior branches of the left bundle as emphasized by Mahaim.<sup>41</sup> Only one, rather atypical, example (Fig. 22) was found of the rare type (Wilson<sup>68</sup>) as judged by conventional Leads I and III (chief deflections in Lead I downward; in Lead III upward), and in this instance the semidirect leads indicated the presence of right bundle-branch block.

A very interesting result of the investigation is shown in Fig. 21 A and B. The conventional leads of these two patients show a general similarity, and yet the combined exploratory leads quite definitely show that in Fig. 21 A left ventricular block is present while in Fig. 21 B, there is delay in the activation of the right ventricle. The

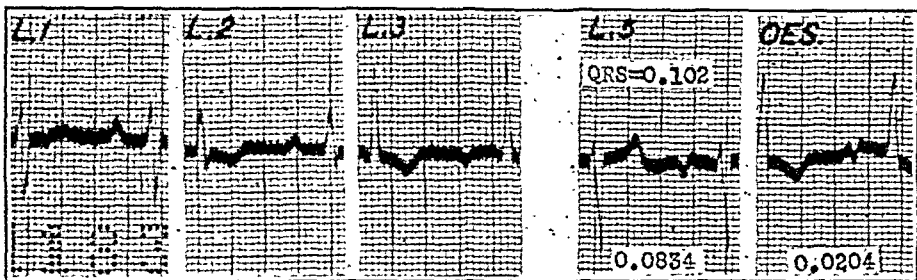


Fig. 22.—Patient R. M. An example of the rare type of bundle-branch block. From left to right, Leads I, II and III, chest Lead V, and juxta-ventricular esophageal lead. The chest lead shows obvious delay in the formation of the intrinsic deflection. The esophageal electrode in this case did not lie close to the left ventricular base, and the upstroke is therefore not a trustworthy indication of a true position of the intrinsic deflection. The conclusion is, however, warranted that this is a case of right ventricular block.

example also shows that bundle-branch block may occur without giving rise to the classical changes in the direction of the T-waves in standard Leads I and III.

*Ventricular Extrasystoles.*—Figure 23 is an example of the common type of bundle-branch block due to delayed activation of the left ventricle. One example of a ventricular extrasystole is marked by a cross in record 5. The time relationships of the onset of the intrinsic deflections in the extrasystolic electrograms are indicated on the record. It is evident that in this particular instance the base of the left ventricle was activated 0.0117 sec. in advance of the right ventricle in contradistinction to the sequence of events in the curve immediately preceding the extrasystole. Such a result leaves no room for doubt that the extrasystole must have arisen from a point in the left ventricle.

The procedure applied in Fig. 20 may be used as a useful method for locating the site of origin of ventricular extrasystoles. One ex-



ample of many studies pursued with this objective in view is illustrated in Fig. 24. The record exhibits curves of ventricular extrasystoles originating from three different foci. That in record 4 presumably arises in the septum, probably on the right side of the heart. It is, however, possible to argue that the triphasic precordial curve has been wrongly interpreted when the intrinsic deflection is assumed to occur at 0.029 sec. and that the true position of the intrinsic deflection in this instance arose nearer 0.086 sec. in the right ventricular area explored. This view is hardly tenable when the records 5 and

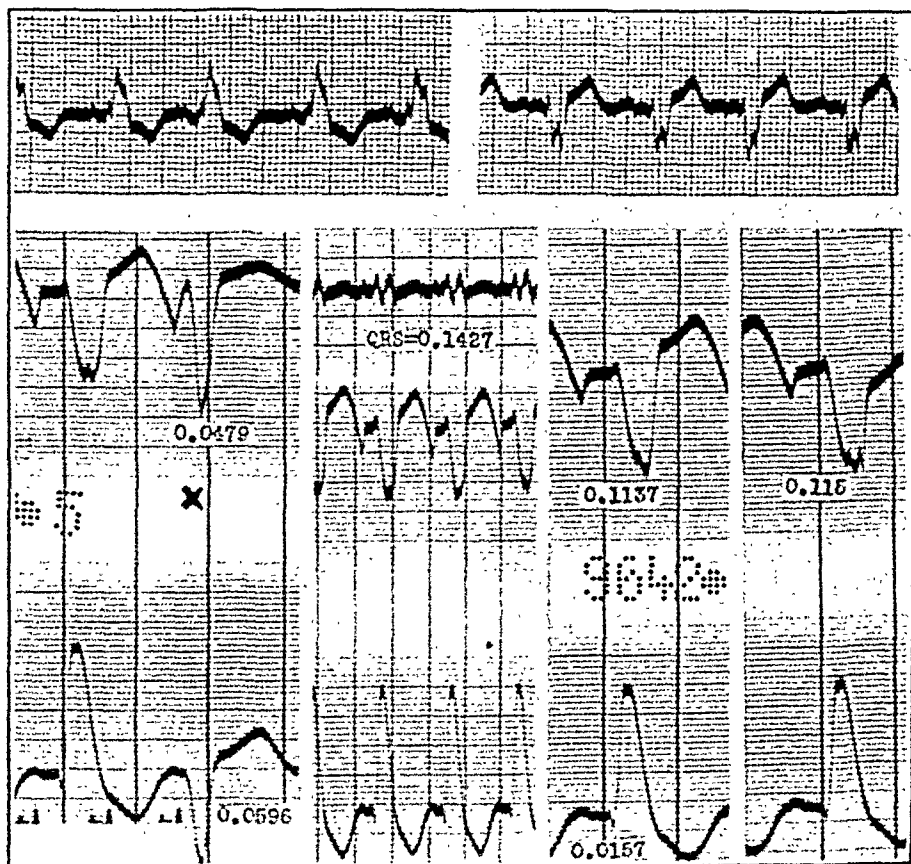


Fig. 23.—Patient B. J. Bundle-branch block of common type. Single string: Leads I and III. Double strings: esophageal curves above and chest curves below: camera at double speed. Triple strings: Lead II above, esophageal curve middle, and chest curve below: camera at usual speed. Numbers refer to onset of intrinsic deflections in decimal fractions of a second. An extrasystole is present in the first double record.

Conclusion: A clear example of left bundle-branch block with an occasional extrasystole, arising in the left ventricle.

7 are examined, for in these the extrasystoles arising from opposite sides of the heart yielded very characteristic changes in the appearance not only of the esophageal but also of the precordial curves. What is even more striking is that the conventional (Lead I) curves should be so similar in form in the presence of extrasystoles from opposite sides of the heart. The results of the adaptation of the esophageal lead to the study of ventricular extrasystoles suggest that

under the procedure described a more accurate conception of the meaning of conventional extrasystolic curves would be the reward of additional work in this field.

*Conclusions on Bundle-Branch Block.*—The employment simultaneously of two trustworthy exploring or semidirect leads to the two ventricles in fourteen cases of intraventricular block has thrown additional light upon the difficulties of accurate interpretation of standard electrocardiograms. The conventional leads of the majority of the cases (thirteen out of fourteen) were of the common type, and ten of these were shown to be associated with delay in activation of the base

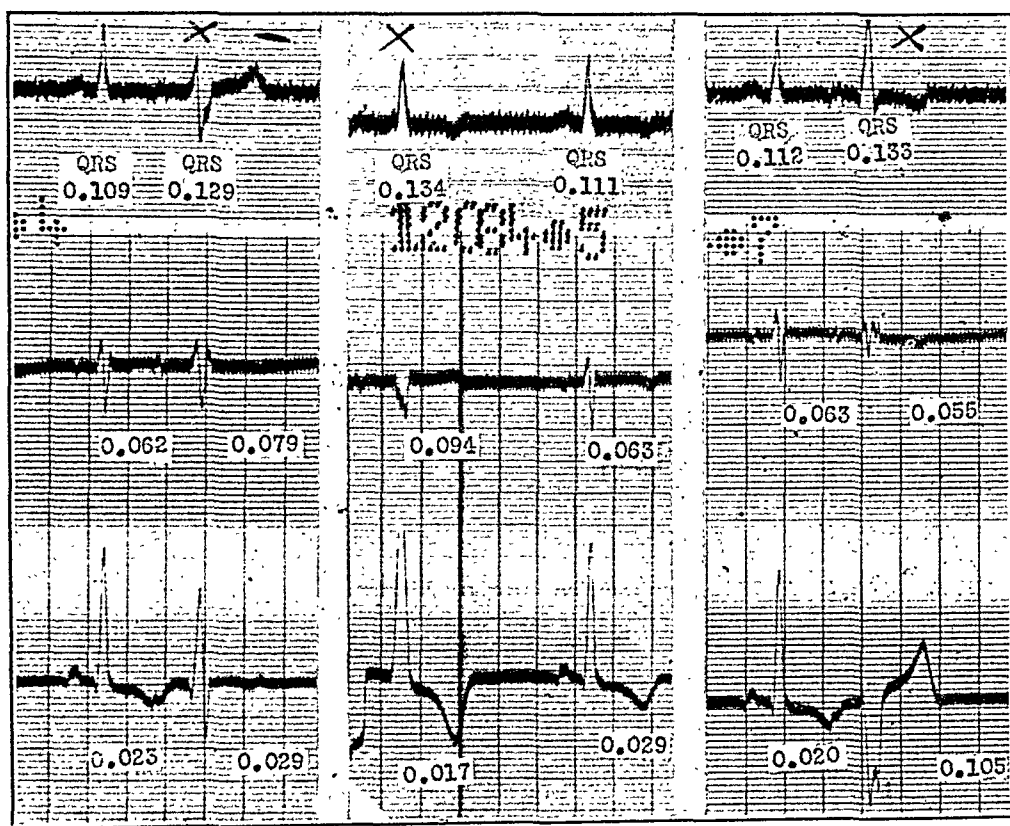


Fig. 24.—Patient M. McC. From a case exhibiting ventricular extrasystoles from three different foci. All three records were obtained with the esophageal electrode lying close to the base of the left ventricle. From above downward in each record are Lead I, an esophageal lead tapping the left ventricle, and a precordial lead over the right ventricle. The extrasystolic curves are indicated by crosses. The numbers in fractions of a second indicate the time of onset of intrinsic deflections. The ectopic beat in record 4, may have arisen from the right side of the septum. In record 5, the origin is clearly in the right ventricle and in record 7, in the left. The sensitivity of the string of the esophageal lead is reduced to one-third normal. In two of the records there is some distortion due to the tuning fork.

of the left ventricle. One fairly typical case of the rare type was due to right ventricular block. The occurrence of bundle-branch block does not necessarily give rise to "opposing T-waves." Right bundle-branch block may be present in cases showing conventional curves of the common type and therefore very likely occurs more often than is usually admitted under the new terminology. Two cases of the common type (as judged by the appearances of records of conventional Leads I and III) were probably of a "mixed" or "partial" variety.

Interpretations relying only on the basis of the directions of the main deflections in standard Leads I and III are not always reliable in indicating the site of the responsible lesion in bundle-branch block.

*Summary of Section 5.*—1. The reliability of the esophageal method when used as a semidirect or exploring lead to the left ventricle is discussed in the light of theoretical and experimental data.

2. The current interpretations of standard electrocardiographic leads in cases of bundle-branch block are set forth.

3. The results of employing simultaneous semidirect leads<sup>6</sup> with electrodes over the right and the left ventricles in bundle-branch block are illustrated and discussed.

4. Certain conclusions have been reached in view of the results obtained in a study of fourteen cases of intraventricular block.

5. The adaptation of simultaneous leads to the study of ventricular extrasystoles has yielded suggestive results.

#### GENERAL RECAPITULATION

The validity of using an electrode placed in the esophagus in clinical electrocardiography has been discussed at length in Section 1. On anatomical, theoretical, and experimental grounds the conclusion has been reached that, under the described procedure, the method may legitimately be applied to the human subject. In Sections 2 and 4 the findings in fifteen normal control subjects have provided the foundations upon which a detailed interpretation of the curves obtained by the esophageal lead have been based. As a result of experimental procedures on human and canine subjects, the conclusion has been reached that the esophageal lead is a trustworthy "exploring" or semidirect method. In this rôle it is subject to the general laws governing the employment of semidirect leads. The curves obtained by the method have been designated as "esophageal electrograms" since it has been shown that they have essentially the same characteristics as curves obtained by direct leads from the epicardial surface of the heart. The outstanding feature of esophageal electrograms is the demonstration of "intrinsic deflections" which signal the time of activation of the small areas of heart muscle lying immediately adjacent to the electrode.

The method has been applied to the study in 127 patients at the Johns Hopkins Hospital, exhibiting a wide range of cardiac disorders.

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\*The chest leads used in this study have without exception been derived with the right arm terminal on the precordium and the left leg terminal on the left leg. This arrangement ensures that electronegativity in the records obtained by the lead is indicated by an upward deflection. The use of the chest lead in an exploring rôle emphasizes the importance of maintaining this arrangement in spite of the recent agitation favoring a reversal of the electrodes in order to secure uniformity with the general appearance of the standard derivations. It is particularly desirable that the direction of the intrinsic deflections as obtained by all varieties of semidirect and direct leads employed in animal experimentation and clinical electrocardiography should conform to one rule.

The findings in 35 of these cases have been used in Sections 3 and 5 as a basis for discussion of the Ta-wave, ectopic auricular and ventricular extrasystoles, and bundle-branch block. The suggestion has been made that the esophageal lead may prove to be an aid to the location of the approximate site of origin of ectopic beats. Information of a precise character has been forthcoming with respect to the duration of the T-wave of the auricle in the human subject and its effect on conventional electrocardiograms. The findings in intraventricular delay largely support the new terminology although certain unexpected results and some examples of "mixed block" throw doubt upon the trustworthiness of the criteria which have generally been applied to the interpretation of bundle-branch block in man.

#### GENERAL SUMMARY OF PART I

I. From a theoretical and practical standpoint the validity of the use of the esophageal electrode as a type of semidirect lead in clinical electrocardiography has been established.

II. The results of employing the method in fifty human subjects have been recorded, analyzed and discussed.

#### REFERENCES

1. Ader, M.: Sur un nouvel appareil enregistreur pour câbles sousmarins, *Compt. rend. Acad. d. Sciences de Paris* 124: 1440, 1897.
2. Baetjer, A. M., and McDonald, C. H.: The Relation of Sodium and Calcium Ions to the Heart Rhythmicity, *Am. J. Physiol.* 99: 666, 1931-32.
3. Bakker, N. C.: Analyse des Elektrokardiogramms auf Grund von am Aalherzen ausgeführten Untersuchungen, *Ztschr. f. Biol.* 59: 335, 1912-13.
4. Barker, P. S., Macleod, A. G., Alexander, J., and Wilson, F. N.: The Excitatory Process in the Exposed Human Heart, *Tr. A. Am. Physicians* 44: 125, 1929.
5. Boden, E.: Beobachtungen ueber eine Nachschwankung des Vorhofselektrokardiogramms am isolierten Säugetier- und Menschenherzen, *München. med. Wchnschr.* 68: 1104, 1921.
6. Boden, E., and Neukirch, P.: Elektrokardiographische Studien am isolierten Säugetier- und Menschenherzen bei direkter und indirekter Ableitung, *Pflugers Arch. f. d. ges. Physiol.* 171: 146, 1918.
7. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, *Arch. Int. Med.* 13: 803, 1914.
8. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated With Sclerosis of the Atrio-ventricular Bundle Branches and Their Terminal Arborisations, *Arch. Int. Med.* 22: 331, 1918.
9. Craib, W. H.: A Study of the Electrical Field Surrounding Active Heart Muscle, *Heart* 14: 71, 1927.
10. Cremer, M.: Ueber die direkte Ableitung der Aktionsströme der menschlichen Herzens vom Oesophagus und ueber das Elektrokardiogramm des Foetus, *München. med. Wchnschr.* 53: 811, 1906.
11. Cunningham, A.: *Textbook of Anatomy*, New York, 1917, Revised ed. 4, William Wood and Co., pp. 1150-1153.
12. De Jongh, C. L.: Die Zeitverhältnisse zwischen Elektro- und Mechanokardiogramm, *Pflugers Arch. f. d. ges. Physiol.* 213: 216, 1926.
13. Eiger, M.: Die physiologischen Grundlagen der Elektrokardiographie, *Bull. d. l'Acad. d. sciences de Cracovie*, p. 531, 1911.
14. Eiger, M.: Die physiologischen Grundlagen des Elektrokardiographie, *Pflugers Arch. f. d. ges. Physiol.* 151: 1, 1913.
15. Einthoven, W.: Ein neues Galvanometer, *Annalen der Physik* 12: 1059, 1903.
16. Einthoven, W.: The Relation of Mechanical and Electrical Phenomena of Muscular Contraction With Special Reference to Cardiac Muscle, *Harvey Lectures*, 1924-25, p. 111.

17. Eppinger, H., and Rothberger, C. J.: Ueber die Folgen der Durchschneidung der Tawarasehen Schenkel des Reizleitungssystems, *Ztschr. f. klin. Med.* 70: 1, 1910.
18. Eppinger, H., and Stoerk, O.: Zur klinik des Elektrokardiogramms, *Ztschr. f. klin. Med.* 71: 157, 1910.
19. Eycleshymer, A. C., and Schoemaker, D. M.: *A Cross-Section Anatomy*, New York, 1911, D. Appleton and Co., Sections 24-27, incl.
20. Eyster, J. A. E., and Meek, W. J.: The Interpretation of the Normal E. C. G.: A Critical and Experimental Study, *Arch. Int. Med.* 11: 204, 1913.
21. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch. Int. Med.* 25: 146, 1920.
22. Fredericq, H.: Sur la nature de la systole de l'oreillette, *Arch. internat. d. physiol.* 12: 66, 1912.
23. Hering, H. E.: Experimentelle Studien an Säugethieren über das Elektrokardiogramm, *Arch. f. d. ges. Physiol.* 127: 155, 1909.
24. Hering, H. E.: Ueber die Finalschwankung (Ta Zucke) des Vorhofselektrogramms, *Pflügers Arch. f. d. ges. Physiol.* 144: 1, 1912.
25. Kahn, R. H.: Beiträge zur Kenntniss des Elektrokardiogrammes, *Arch. f. d. ges. Physiol.* 126: 197, 1909.
26. Kahn, R. H.: Elektrokardiogrammstudien, *Arch. f. d. ges. Physiol.* 140: 627, 1911.
27. Kraus, F., and Nicolai, G.: *Das Elektrokardiogramm des gesunden und kranken Menschen*, Leipzig, 1910, Veit and Co.
28. Kraus, F., and Nicolai, G.: Ueber das Elektrokardiogramm unter normalen und pathologischen Verhältnissen, *Berlin klin. Wchnschr.* 64: 765 and 811, 1907.
29. Kraus, F., and Nicolai, G.: Ueber die funktionelle Solidarität der beiden Herzhälften, *Deutsche med. Wchnschr.* 1: 1, 1908.
30. Lieberman, A., and Liberson, F.: An Internal Electrocardiographic Lead, *Proc. Soc. Exp. Biol. & Med.* 31: 441, 1934.
31. Lewis, T.: Polarizable as Against Non-polarizable Electrodes, *J. Physiol.* 49: 50-52, 1915 (Proc.).
32. Lewis, T.: *The Mechanism and Graphic Registration of the Heart Beat*, ed. 3, London, 1925, Shaw and Sons.
33. Lewis, T.: On the Electrocardiographic Curves Yielded by Ectopic Beats Arising in the Walls of the Auricles and Ventricles, *Brit. M. J.* 1: 750, 1910.
34. Lewis, T.: The Pacemaker of the Mammalian Heart as Ascertained by Electrocardiographic Curves, *J. Physiol.* 41: 11, 1910-11 (Proc.).
35. Lewis, T.: Ectopic Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature: The Pacemaker of the Heart, *Heart* 2: 23, 1910-1911.
36. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Parts I-V. *Phil. Trans. Roy. Soc., B*, CCVII, 221, 1916.
37. Lewis, T., in collaboration with Feil, H. S., and Stroud, W. D.: A Polymyograph and a Comparison of the Contraction and Excitation Waves in the Mammalian Auricle, *Heart* 7: 131, 1918-20.
38. Lewis, T., Meakins, J., and White, P. D.: The Excitatory Process in the Dog's Heart. Part I. The Auricles, *Phil. Trans. Roy. Soc., B*, CCV, 375, 1914.
39. Lewis, T., Oppenheimer, A., and Oppenheimer, B. S.: The Site of Origin of the Mammalian Heart Beat: The Pacemaker in the Dog, *Heart* 2: 147, 1910.
40. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II. The Ventricle, *Phil. Trans. Roy. Soc., B*, CCVI, 181, 1915.
41. Mahaim, I.: *Les maladies organiques du faisceau de His-Tawara (étude clinique et anatomique)*, Paris, 1931, Masson et Cie.
42. Max, L. W.: The Time Relations of the Electrical and Mechanical Response of Heart Muscle, *Am. J. Physiol.* 98: 318, 1931.
43. Mines, G. R.: Some Observations on Electrograms of the Frog's Heart (Preliminary Note), *Proc. Camb. Phil. Soc.* 16: 615, 1912.
44. Minkowski, O.: Die Registrierung der Herzbewegungen am linken Vorhof, *Deutsche med. Wchnschr.* 32: 1248, 1906.
45. Nörr, J.: Das Elektrokardiogramm des Pferdes, seine Aufnahme und Form, *Ztschr. f. Biol.* 61: 197, 1913.
46. Noyons, A. K. M.: Communications About the Electrocardiogram of the Atrium Cordis, *Onderzoek g. i. h. Physiol. lab. Utrecht v. Reeks* 11: 214, 1910.
47. Oppenheimer, B., and Pardee, H. E. B.: The Site of the Cardiac Lesion in Two Instances of Intraventricular Block, *Proc. Soc. Exper. Biol. & Med.* 17: 177, 1920.

48. Pardee, H. E. B.: Concerning the Electrodes Used in Electrocardiography, *Am. J. Physiol.* 44: 80, 1917.
49. Piersol, J. A.: Human Anatomy, Philadelphia and London, 1930, J. B. Lippincott and Co., p. 714, Fig. 675.
50. Rothberger, C. J.: Zur Diagnose des Schenkelblocks, *Ztschr. f. klin. Med.* 123: 460, 1933.
51. Rothberger, C. J., and Winterberg, H.: Studien ueber die Bestimmung des Ausgangspunktes ventriculärer Extrasystolen mit Hilfe des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* 154: 571, 1913.
52. Rothberger, C. J., and Winterberg, H.: Zur Diagnose der einsertigen Blockierung der Reizleitung in den Tawara'schen Schenkeln, *Zentralbl. f. Herzkrankh.* 5: 206, 1913.
53. Rothberger, C. J., and Winterberg, H.: Experimentelle Beiträge zur Kenntnis die Reizleitungsstörungen in den Kammern des Säugetierherzens, *Ztschr. f. d. ges. exper. Med.* 5: 264, 1917.
54. Rümke, H. C.: Sur quelques électrogrammes de lambeaux du muscle cardiaque de la grenouille, *Arch. Neerland. d. physiol. de l'homme et des animaux* 1: 161, 1918.
55. Samojloff, A.: Elektrokardiogrammstudien, *Beitr. z. Physiol. u. Pathol. v. O. Weiss*, 1908, p. 171. Also, Elektrokardiogramme, *Samml. anat. u. physiol. Vorträge u. Aufsätze (Gaupp and Nagel)* Jena 2: 1, 1909.
56. Samojloff, A.: Weitere Beiträge zur Elektrophysiologie des Herzens, *Arch. f. d. ges. Physiol.* 135: 417, 1910.
57. Selenin, W. P.: Das Elektrokardiogramm und die pharmakologischen Mittel aus der Gruppe des Digitalis und des Digitoxins, *Arch. f. d. ges. Physiol.* 143: 137, 1912.
58. Sprague, H. B., and White, P. D.: Clinical Observations on the T-Wave of the Auricle Appearing in the Human Electrocardiogram, *J. Clin. Investigation* 1: 389, 1925.
59. Straub, H.: Zur Analyse des Elektrokardiogramms (nach Versuchen am isolierten Froschherzen), *Ztschr. f. Biol.* 53: 499, 1910.
60. Waller, A.: On the Electromotive Changes Connected With the Beat of the Mammalian Heart and of the Human Heart in Particular, *Phil. Trans. Roy. Soc., London* 180: 169, 1889.
61. Wedd, A. M., and Stroud, W. D.: The Spread of the Excitation Wave Related to the Standard Electrocardiogram in the Dog's Heart, *Heart* 9: 15, 1921-22.
62. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, *Tafelband*, Leipzig, 1927, Wm. Englemann.
63. Wiedemann, G.: Das Elektrogramm des Vorhofes beim Hund, *Beitr. z. Physiol.* 1: 337, 1920.
64. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heartbeat Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1929-30.
65. Wilson, F. N., Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *AM. HEART J.* 9: 472, 1933-34.
66. Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, *AM. HEART J.* 9: 459, 1933-34.
67. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1933-34.
68. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1931-32.
69. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by the Heart Muscle and Other Excitable Tissues, *University of Michigan Studies, Scientific Series X*, 1933, pp. 1-57. Also in curtailed form in *J. Gen. Physiol.* 16: 423, 1933.
70. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart at the Apices of Einthoven's Triangle, *AM. HEART J.* 7: 207, 1931-32.
71. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, *AM. HEART J.* 6: 637, 1930-31.
72. Wood, F. C., and Wolferth, C. C.: Experimental Coronary Occlusion: Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium: An Electrocardiographic Study, *Arch. Int. Med.* 51: 771, 1933.

## THROMBO-ANGIITIS OBLITERANS AND TOBACCO

### THE INFLUENCE OF SEX, RACE, AND SKIN SENSITIVITY TO TOBACCO ON CARDIOVASCULAR RESPONSES TO SMOKING\*

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FROM clinical observations over a period of many years physicians have known that tobacco smoking was harmful to patients with thrombo-angiitis obliterans.<sup>1, 2</sup> A reason for the injurious effect was pointed out when, by means of skin temperature changes, we showed that tobacco smoking produced vasoconstriction of the vessels of the extremities<sup>3, 4</sup>; this process further decreasing the already impaired peripheral circulation of these individuals. This finding was corroborated and additional information was furnished by the work of Barker,<sup>5</sup> Wright and his associates,<sup>6, 7, 8</sup> and others.<sup>9, 10</sup>

Our investigation was continued to determine whether the observed cardiovascular effects of tobacco smoking had any peculiar features which might explain some of the unusual characteristics of thrombo-angiitis obliterans. Among the diseases in which tissues common to both sexes are involved, with the exception of hemophilia, no other condition shows the same almost entire predilection for males. Also, the frequency of the disease among individuals of the Jewish race is unusual. To throw some possible light on these oddities, the peripheral skin temperature, the pulse rate, and the blood pressure responses of male and female subjects and of Jewish and of gentile subjects to tobacco smoking were studied.

A second point of interest resulted from the excellent work on hypersensitivity to tobacco by Harkavy and his associates<sup>11</sup> and Sulzberger,<sup>12</sup> who showed that nearly 80 per cent of their group of patients with thrombo-angiitis obliterans gave an allergic skin reaction to tobacco; while less than half that number of responses was obtained among normal subjects. Sulzberger considers the evidence to be highly suggestive that thrombo-angiitis obliterans is connected in some way with a hypersensitivity to tobacco, since in agreement with his experimental data he finds many clinical features of thrombo-angiitis obliterans which are common to other allergies. It is known, for example, that certain allergens involve certain tissues and even that tissue in certain definite areas only. Thus tobacco may affect the vascular apparatus, especially in the extremities, and produce changes in the blood vessels themselves and the tissues supplied by them. We were interested in knowing whether individuals who showed a skin sensitivity to tobacco extract

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had a greater peripheral vasoconstrictor effect from tobacco smoking than individuals who were not skin sensitive.

#### PROCEDURE.

All of the healthy young adult subjects were studied under the same conditions. The males were medical students who smoked from fifteen to twenty cigarettes a day. The use of cigarettes by the females was not so uniform. No smoking was permitted for a period of three hours before the test. To keep normal peripheral vasoconstriction at a minimum,<sup>4</sup> the room in which the study was carried out was kept at a temperature of  $85^{\circ}\text{F.} \pm 3^{\circ}$ . In order that the skin temperatures of the subjects, who were studied lying on a comfortable bed, could rapidly reach an adjustment to the environmental conditions, their arms and legs were bared while their trunks were covered with only single sheets. The smoking period for two cigarettes of the standard brand used throughout the test was twenty minutes. Usually two-thirds of one cigarette was consumed in from seven to nine minutes, then there was a pause for two or three minutes, then a second cigarette was smoked in the same time as the first one. Skin sensitivity to tobacco was determined by the intradermal technic. The tobacco solution was a composite one combining several different brands of tobacco. Coca's control solution was used on the opposite forearm. The reaction was considered to be one-plus when the original wheal enlarged to from 8 to 11 mm. in diameter, two-plus from 12 to 14 mm., three-plus from 14 to 17 mm., four-plus from 17 mm., or any size above, or the development of pseudopods. At five-minute intervals the skin temperatures of the tips of the left fingers and toes were recorded with a Tycos dermaterm, the blood pressure in the right arm was taken with a standard sphygmomanometer, and the pulse rate was counted for one-half minute.

#### DATA AND COMMENT

A typical example of the decrease in the peripheral skin temperature and increase in blood pressure and pulse rate on smoking is shown in Fig. 1. The data from a study of twenty-nine subjects are given in Table I.

*Influence of Sex.*—Cigarette smoking produced a decrease in the skin temperatures of the fingers and toes and an increase in the pulse rates and blood pressures in women to the same degree that it did in men.

In the light of the relation of tobacco smoking to thrombo-angiitis obliterans this fact offered no explanation as to why the disease shows the marked predilection for males. If smoking is the cause of thrombo-angiitis obliterans, one would expect to see this disease appear more frequently in women in the future because there is no doubt but that they are smoking more than did past generations of their sex. On the other hand, the possibility of a sex hormone in some way protecting the



TABLE I  
SUMMARY OF CARDIOVASCULAR EFFECTS OF SMOKING TWO CIGARETS

SUBJECT NUMBER	AGE	DAILY USE OF CIGARETS	INHALES	SKIN SENSITIVITY TO TOBACCO	DECREASE IN AVERAGE SKIN TEMP. OF FINGERS	DECREASE IN AVERAGE SKIN TEMP. OF TOES	INCREASE IN PULSE RATE PER MIN.	INCREASE IN BLOOD PRESSURE (M.M. HG.) SYSTOLIC      DIASTOLIC
<i>Males—Gentiles</i>								
1	25	15	D*	Neg.	0.4° C.	1.2° C.	22	6      8
2	26	20	D	Neg.	1.1	3.4	16	8      6
3	23	20	D	Neg.	1.2	0.9	18	12      6
4	23	15-20	M	Neg.	1.2	1.1	22	24      16
5	24	15	M	Neg.	0.3	1.2	18	14      20
6	22	15-20	M	Neg.	0.8	1.0	16	16      14
<i>Average</i>					0.8	1.5	19	13      12
7	23	20	D	+++	0.5	2.5	10	12      10
8	21	15	D	+++	0.5	1.4	12	6      6
9	33	20	M	+	2.1	2.5	14	16      12
10	23	15	M	+++	1.1	1.7	16	14      16
11	26	24	M	++	0.8	1.9	14	16      6
12	23	15-20	M	+++	0.3	1.8	14	10      8
<i>Average</i>					0.9	2.0	13	12      10
<i>Males—Jewish</i>								
13	25	25-30	D	Neg.	0.9	2.3	24	14      6
14	26	30	D	Neg.	2.4	2.9	12	12      8
15	24	35-40	D	Neg.	4.6	4.0	24	18      10
16	23	15	M	Neg.	1.5	2.3	24	10      14
17	23	15	M	Neg.	2.8	3.7	28	8      12
18	23	15-20	M	Neg.	0.6	0.9	16	18      14
19	25	10-12	S	Neg.	1.4	4.8	14	10      12
<i>Average</i>					2.0	3.0	20	13      11

\*D = Deeply  
M = Moderately  
S = Slightly

TABLE I—CONT'D

SUBJECT NUMBER	AGE	DAILY USE OF CIGARETTES	INHALES	SKIN SENSITIVITY TO TOBACCO	DECREASE IN AVERAGE SKIN TEMP. OF FINGERS	DECREASE IN AVERAGE SKIN TEMP. OF TOES	INCREASE IN PULSE RATE PER MIN.	INCREASE IN BLOOD PRESSURE (MM. HG.)	
								SYSTOLIC	DIASTOLIC
20	25	15	M	+++	1.9	4.3	12	10	10
21	25	20	M	++++	1.2	1.6	20	20	8
22	22	20	D	++	5.4	3.2	18	16	20
<i>Average</i>					2.8	3.0	17	15	13
<i>Females—Gentile</i>									
23	27	2-3	S	Neg.	1.5	2.3	16	10	14
24	35	2-3	S	Neg.	0.8	0.8	14	8	12
25	22	10-12	M	Neg.	2.2	2.8	20	10	8
26	22	10	M	Neg.	2.4	3.1	30	14	16
27	16	8-10	M	Neg.	1.6	2.0	12	22	12
28	18	10-15	M	Neg.	0.6	1.6	24	12	16
29	20	10-15	M	Neg. +	1.6	3.6	14	16	18
<i>Average</i>					1.5	2.3	19	13	14

females must be kept in mind, since McGrath<sup>13</sup> has shown that large doses of theelin kept female rats from developing gangrene of the tail when toxic quantities of ergotamine tartrate, a vasoconstrictor substance, were given.

*Influence of Race.*—The average decrease in the skin temperatures of the fingers and toes and the average increase in blood pressures and pulse rates were greater for the Jewish males than for the gentile males. The difference was particularly more marked in the skin temperature changes.

The reason for this difference between the two groups is not entirely apparent. It would be easy to assert that this fact is responsible for

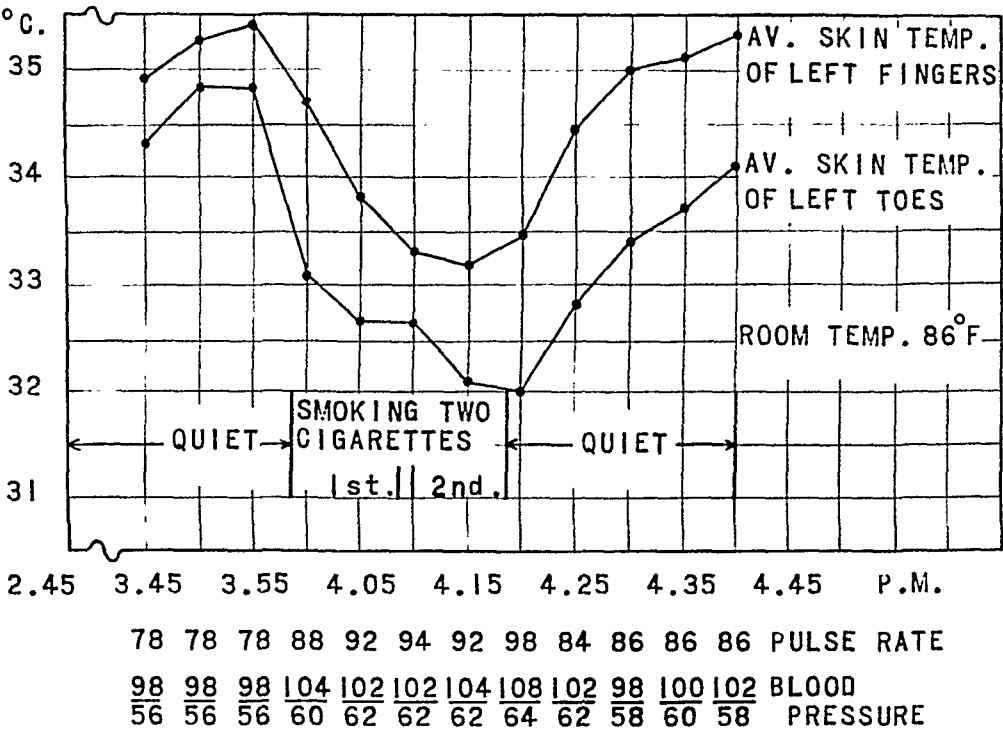


Fig. 1.—Decrease in the skin temperature of the fingers and toes and increase in pulse rate and blood pressure of Subject 25, female, on the smoking of two cigarets.

the greater incidence of thrombo-angiitis obliterans in Jews than in other elements of the population; but tobacco smoking has not been definitely established as the cause of that disease. It is possible that a simpler reason is the true one. We were impressed by the fact that the smoking of the Jewish subjects was more intensive, was quicker, and with deeper inhalations than that of the gentile subjects. This temperamental difference may be the factor accounting for the greater cardiovascular response among Jews, since slow smoking and simple puffing rather than inhaling is known to produce a lesser effect.<sup>4</sup> Hypersensitivity to tobacco could not have been the cause of the race difference, as skin reactions to tobacco were twice as frequent among the gentiles as among the Jews.

*Influence of Hypersensitivity to Tobacco.*—There was no consistent difference in the skin temperatures, the blood pressure, and pulse rate response to smoking between individuals who showed skin sensitivity to tobacco and those who did not. In accord with this, among the sensitive individuals there was no correlation between the degree of the skin reaction and the cardiovascular response. This finding is a corroboration of a preliminary report on the same question by Wright and Moffat.<sup>5</sup>

We consider the lack of relationship between skin sensitivity to tobacco and the cardiovascular response to smoking to be due to the fact that the two effects are the result of different components. Sulzberger<sup>12</sup> has emphasized that the reaction of hypersensitivity is produced by a constituent or constituents of tobacco other than nicotine. In contrast to this, we found<sup>4</sup> that nicotine administered intravenously in amounts theoretically absorbed in the smoking of one or two cigarettes produced approximately the same decrease in the skin temperature of the fingers and toes and the same increase in blood pressure and pulse rate as was obtained on the smoking of one or two cigarettes. In further support of the theory that the nicotine component is responsible for the peripheral vasoconstriction, the mechanism by which tobacco smoking causes a drop in the skin temperature of the extremities is of interest. It is claimed<sup>14, 15</sup> that the effect of nicotine is largely brought about through the sympathetic nervous system. That the peripheral vasoconstrictor effect of tobacco observed by us was carried out through the nerve supply to the part, was demonstrated by anesthetizing the test area, the toes, on one foot by a posterior tibial nerve block and obtaining no decrease in their skin temperature on smoking, while the usual decrease occurred in the unanesthetized toes of the other foot. That the sympathetic fibers were the pathways involved was shown by obtaining, on smoking, no decrease in the skin temperature in the toes of a subject who had had a bilateral lumbar sympathetic ganglionectomy, while the usual response occurred in the unaffected fingers. Thus the peripheral vasoconstrictor effect of tobacco smoking is carried out through the same mechanism by which nicotine acts.

It is not necessary to consider the allergic possibilities of tobacco to understand its aggravating action in thrombo-angiitis obliterans. In a disease which is characterized by a deficiency in circulation due to thromboses and in which a substance is known clinically to be detrimental, the production of vasospasm by that substance would seem to be a significant effect and much more direct than an allergic effect. The vasoconstrictor effect is so pertinent to this occlusive arterial disease that one cannot say definitely that tobacco is not the exciting cause of thrombo-angiitis obliterans, as it is claimed to be by Silbert.<sup>2</sup> Other vasoconstricting substances, pituitrin,<sup>16</sup> and particularly ergot<sup>17</sup> have

been responsible for peripheral gangrene. There is thus considerable evidence that prolonged or marked vasoconstriction may initiate organic vascular occlusions.

Gaps still exist in the knowledge of thrombo-angiitis obliterans, but the fact has been established that cigaret smoking reduces the blood supply to the extremities; and one should not hesitate to present the reasons for the avoidance of tobacco and to order "no smoking" by patients with that disease.

#### SUMMARY

1. The smoking of two cigarets by women resulted in a drop in the skin temperatures of their fingers and toes, and in an increase in their blood pressures and pulse rates similar to those observed in men.

2. Such cigaret smoking by Jewish males caused a greater drop in the skin temperatures of their fingers and toes than occurred in gentile males. This fact may be of significance in accounting for the greater incidence of thrombo-angiitis obliterans among Jews than among other elements of the population.

3. No relationship was found between skin sensitivity to tobacco and its cardiovascular effect on smoking.

#### REFERENCES

1. Erb, W.: Ueber Dysphagia Angiosclerotica. München. med. Wehnschr. 51: 905, 1904.
2. Silbert, S.: Thrombo-angiitis Obliterans: Treatment of 524 Cases by Repeated Intravenous Injections of Hypertonic Salt Solution, Surg. Gynec. Obst. 61: 214, 1935.
3. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco Demonstrated by Skin Temperature Changes, Proc. Soc. Exper. Biol. & Med. 29: 487, 1932.
4. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-angiitis Obliterans, Ann. Surg. 98: 70, 1933.
5. Barker, N. W.: Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet., Mayo Clin. 8: 281, 1933.
6. Wright, I. S.: The Clinical Value of Human Capillary Studies in Fever, Mental Deficiency, Nephritis, Vascular Diseases, Clubbed Fingers, Tobacco Smoking and Argyria, J. A. M. A. 101: 439, 1933.
7. Duryee, A. W., and Wright, I. S.: Modern Methods for the Study of Human Capillaries, Am. J. M. Sc. 185: 664, 1933.
8. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral Vascular System, J. A. M. A. 103: 318, 1934.
9. Johnson, H. J., and Short, J. J.: Effect of Smoking on Skin Temperature, J. Lab. & Clin. Med. 19: 962, 1934.
10. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, J. A. M. A. 104: 1963, 1935.
11. Harkavy, J., Hebal, S., and Silbert, S.: Tobacco Sensitiveness to Thrombo-angiitis Obliterans, Proc. Soc. Exper. Biol. & Med. 30: 104, 1932.
12. Sulzberger, M. B.: Recent Immunologic Studies in Hypersensitivity to Tobacco, J. A. M. A. 102: 11, 1934.
13. McGrath, E. J.: Experimental Peripheral Gangrene, J. A. M. A. 105: 854, 1935.
14. Cushing, A. E.: Pharmacology and Therapeutics, Philadelphia, 1918, Lea and Febiger, p. 308.
15. Sollmann, T.: A Manual of Pharmacology, Philadelphia, 1917, W. B. Saunders Company, p. 406.
16. Holselaw, F. M., and Booth, J. A.: Symmetrical Gangrene Following Excessive Dose of Pituitrin, Arch. Pediat. 42: 64, 1925.
17. Kaunitz, J.: The Pathological Similarity of Thrombo-angiitis Obliterans and Endemic Ergotism, Am. J. Path. 6: 299, 1930.

# THE RELATION OF THE SYSTOLIC BLOOD PRESSURE AND HEART RATE TO ATTACKS OF ANGINA PECTORIS PRECIPITATED BY EFFORT\* †

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**A**LTHOUGH angina pectoris is a disorder of the cardiovascular system, our knowledge of the changes in the circulation accompanying attacks is very meager. The standardized exercise tolerance test recently described<sup>27</sup> affords a means of inducing typical paroxysms of angina and makes possible accurate measurement of the heart rate and blood pressure during various phases of the paroxysms.

Measurements of the heart rate and systolic blood pressure were made in thirty-five patients before and during induced attacks of angina, in order to learn whether the changes which occurred were of any diagnostic or etiological importance and to learn whether the disappearance of angina pectoris following total thyroidectomy was dependent on a diminished internal secretion of adrenalin.

## METHODS

Attacks of angina pectoris were induced by exercise under standard conditions according to the method previously described.<sup>27</sup> The test was performed in a room maintained at a temperature between 45 and 55° F. The exercise consisted of repeatedly mounting and descending a staircase made up of two steps, each nine inches high; the duration of exercise being limited in each patient by the development of anginal pain. The patients were allowed to work at a rate which was natural and comfortable for them.

All patients were accustomed to the test and the apparatus before the measurements were made. The number of trips and the duration of exercise which induced angina in these tests did not differ appreciably from that required when determining the exercise tolerance of the same patients without the apparatus for determining blood pressure and heart rate.

The resting heart rate and systolic blood pressure were measured at one-minute intervals with the patient standing at ease; thereafter measurements were made at one-half-minute intervals throughout the exercise, during the induced attack of angina, and during the period of recovery. The systolic blood pressure was determined by palpation, using a standard cuff attached to the right arm and connected by rubber

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tubing to a mercury manometer on a nearby table. The results obtained by this method were found to agree satisfactorily with measurements of the blood pressure obtained by the auscultatory method during exercise on the staircase or on the bicycle ergometer. The heart rate was obtained by the use of a stethoscope strapped to the precordium, the number of beats in fifteen seconds being counted. The results obtained by this method were found to agree satisfactorily with simultaneous heart rate measurements obtained from electrocardiographic tracings obtained during exercise. Duplicate determinations on different days revealed only minor variations in the heart rate and blood pressure curves.

Measurements made using the bicycle ergometer showed the same types of changes in heart rate and systolic blood pressure as were observed when angina was induced by exercise on the two-step staircase. Because of the difference in the two types of work, however, there are differences in the actual heart rate and blood pressure readings obtained by these two methods.

#### RESULTS

Thirty-five patients who developed angina pectoris on exertion and fifteen individuals of similar age (forty-five to sixty-five years), but with no evidence of heart disease, were studied. Measurements made before and after entering the cold room showed that the temperature had no appreciable effect on either the heart rate or the blood pressure.

The number of trips necessary to induce angina in the different patients ranged from nine to sixty-four. Ten of the thirty-five patients with angina developed a typical attack after less than two minutes of exercise; fourteen exercised from two to three minutes before pain forced them to stop; and the remaining eleven were able to exercise for three and one-third to four and one-half minutes. The rate of exercise was twelve to eighteen trips per minute in twenty-one patients, nine to eleven trips per minute in twelve patients, and twenty to twenty-two trips per minute in two patients.

TABLE I  
THE INCREASE IN HEART RATE WITH ATTACKS OF ANGINA PECTORIS

INCREASE IN HEART RATE (BEATS PER MIN.)	AT ONSET OF ANGINAL ATTACK (NUMBER OF CASES)	DURING ATTACKS* (NUMBER OF CASES)
-10 to +9	0	3
+10 to +19	0	5
+20 to +29	2	6
+30 to +39	5	8
+40 to +49	9	2
+50 to +59	5	4
+60 to +69	3	2
+70 to +79	4	0
+80 to +89	3	0
Total	31	30

\*One minute after cessation of exercise.

There was no appreciable difference between the curves of heart rate and systolic blood pressure during and after exercise of those patients who developed angina on exertion and those normal persons who undertook the same exertion but who did not develop heart pain.

The heart rate during exercise was studied in thirty-one of the patients with angina pectoris and in thirteen of the persons with no heart disease. In general the heart rate increased steadily during exertion, reached a maximum after approximately two or three minutes of exercise, and decreased rapidly during recovery (Table I). The curves showing the average increase in rate for each half minute of exercise and recovery in thirty-one patients with angina pectoris and ten patients with no heart disease appear in Fig. 1. The rate at which the heart rate increased during exertion varied somewhat in the different patients.

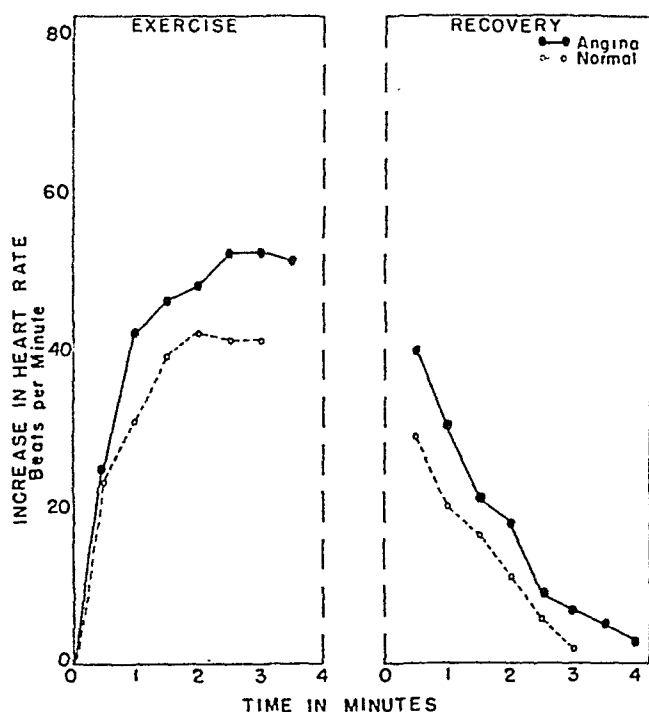


Fig. 1.—The average increase in hear rate during exercise and recovery of thirty-one patients who developed angina pectoris on exertion and in thirteen persons with no evidence of heart disease. The duration of time between the last measurement made during exercise and the first measurement during recovery was 30 seconds.

This variation was apparently unrelated to the variation in the heart rate at rest, the development of angina pectoris, or the speed of exercise in these tests. Although the average increase in heart rate for patients with no evidence of heart disease was slightly less than the average for patients with angina pectoris, individual patients in both groups showed curves which were very similar.

In seventeen of the thirty-one patients with angina pectoris the increase in heart rate for each half minute of exercise was within twelve beats per minute of the average increase for all patients with angina. In these individuals the heart rate, at the time pain developed, was forty to sixty-eight beats per minute greater than the rate at rest. Pa-



tient 29 (Fig. 2) is typical of this group, while D. O., of the normal group, showed a similar response. In six other patients with angina the increments were definitely less than average, so that at the time pain developed the heart rate had increased only 28 to 36 beats per minute. Patient 27 (Fig. 2) of the angina group and J. R., of the normal group, are representative of this type of response. In the remaining eight patients with angina pectoris the heart rate showed a response that was strikingly greater than average. At the time that angina developed the heart rate was 74 to 80 beats per minute higher than the resting level (Patient 23, angina, and E. W., normal, Fig. 2).

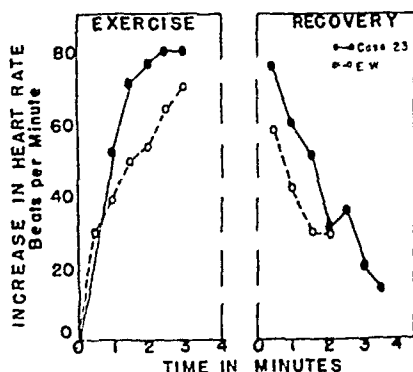
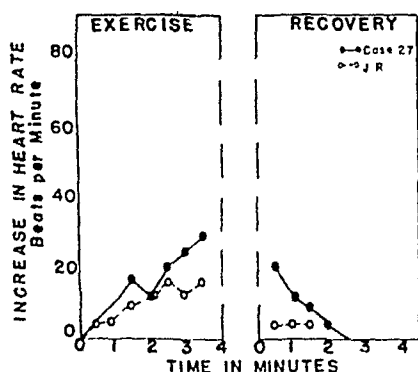
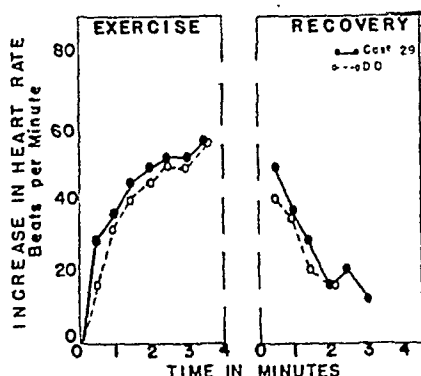


Fig. 2.—Characteristic changes in heart rate during and after exercise in patients who developed angina pectoris on exertion and in persons with no evidence of heart disease. The duration of time between the last measurement made during exercise and the first measurement during recovery was 30 seconds.

The shape of the curve was not altered by the onset of anginal pain. Two patients who developed heart pain and one person with no heart disease showed premature beats during the exercise and for a short time following exertion.

With the cessation of exercise the heart rate decreased rapidly. During the first minute of recovery the average decrease in heart rate was 23 beats per minute. The length of time necessary for the heart to return to the resting rate varied considerably, and, although not determined in all instances, two minutes were required in about one-half the

cases, while in a few instances as long as four and one-half minutes were necessary (Table I). The continuation or rapid disappearance of anginal pain was apparently unrelated to the rate of slowing of the heart.

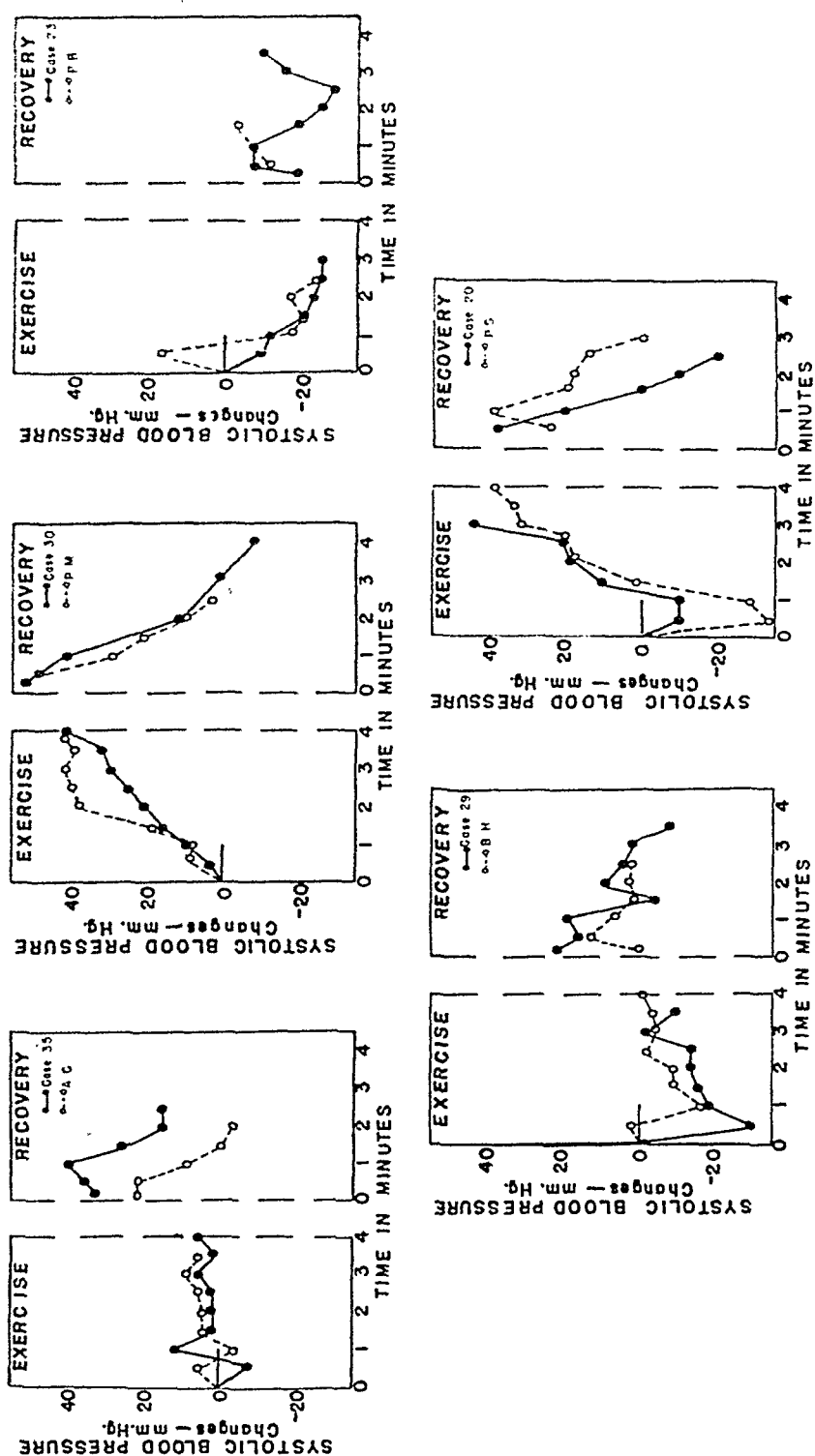


Fig. 3.—Characteristic changes in blood pressure during and after exercise in patients who developed angina pectoris on exertion and in persons with no evidence of heart disease. The duration of time between the last measurement made during exercise and the first measurement during recovery was 30 seconds.

The systolic blood pressure showed five types of response during exercise. The type of response for a given individual was quite constant and was not influenced by the blood pressure during rest nor the rate of exercise. Similar types of response were observed in both the patients

with angina pectoris and those without heart disease. The shape of the curve was not altered by the onset or presence of heart pain.

*Group 1.* In seven patients with angina pectoris there was little or no change during exercise, the blood pressure remaining within 10 mm. Hg of the resting level, e.g., Patient 35, angina pectoris (Fig. 3) and A. C., normal (Fig. 3). *Group 2.* In seven instances the blood pressure gradually increased 16 to 44 mm. Hg above the resting level, e.g., Patient 30, angina pectoris (Fig. 3) and P. M., normal (Fig. 3). *Group 3.* In six patients with angina the blood pressure dropped steadily during exercise, reaching its lowest level (20 to 38 mm. Hg lower than the resting level) when angina developed, e.g., Patient 23 (Fig. 3). Four of these patients developed angina after less than two minutes of exercise; P. B., with no heart disease, showed a similar blood pressure curve (Fig. 3). *Group 4.* Seven patients with angina showed a drop of 10 to 24 mm. Hg during the first minute of exercise, similar to what occurred in Group 3. The pressure then increased, approached, and later exceeded the resting level so that at the time of development of heart pain the pressure was 10 to 44 mm. Hg higher than the level during rest, e.g., Patient 20 (Fig. 3) and P. S. (Fig. 3). *Group 5.* In eight of the thirty-five patients with angina there was an initial drop in pressure during the first minute varying between 16 and 60 mm. Hg similar to Groups 3 and 4. This was followed by a slow and gradual rise which approached, but did not exceed, the resting level despite exercise which continued for as long as four minutes, e.g., Patient 29 (Fig. 3) and B. H. (Fig. 3).

The systolic blood pressure at the onset of the attack was in some cases higher, in others lower, and in many instances essentially the same as the blood pressure during rest (Table II). This variation was brought about by two factors: (1) the changes in blood pressure caused by exercise and (2) the duration of the exercise before being terminated by the onset of pain.

After the cessation of exertion there was usually a sharp rise in the systolic blood pressure, reaching a maximum within the first one and one-half minutes of recovery. This maximum was usually, but not always, higher than the level observed at any time during exercise or during rest (Table II). The blood pressure then gradually fell and returned to the resting level in about one and one-half to four minutes

TABLE II

THE CHANGE IN SYSTOLIC BLOOD PRESSURE WITH ATTACKS OF ANGINA PECTORIS

CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)	AT ONSET OF ANGINAL ATTACK (NUMBER OF CASES)	DURING ATTACK* (NUMBER OF CASES)
+11 to +68	13	26
±10	14	7
-12 to -38	8	1
Total	35	34

\*From 30 to 90 seconds after cessation of exercise.

(Fig. 3). This elevation in systolic blood pressure following exercise was independent of the continuation or disappearance of anginal pain and occurred in patients who did not develop angina on similar exertion.

### *Effect of Total Thyroidectomy*

Changes in systolic blood pressure and heart rate during exercise were studied in eleven patients with angina pectoris before and after total ablation of the thyroid (Table III). In seven of the eleven cases the lowering of the metabolism induced by this procedure was accompanied by relief from symptoms as evidenced by the clinical history and an increase in exercise tolerance. Three of these seven patients (Cases 17, 30, 33) were able to exercise indefinitely without experiencing angina, the test being discontinued usually after ten to twenty minutes of work. The remaining four patients (Cases 32, 27, 12, 3) developed no angina but were forced to stop because of fatigue after performing more than twice as much exercise as was possible before operation. In four patients (Cases 5, 10, 24, 25) there was little or no improvement as judged by the clinical history and the exercise tolerance test. These individuals had low basal metabolic rates or other signs of low metabolism before operation. Experience has shown that such patients are not helped by thyroidectomy, for further lowering of the metabolism is not compatible with comfort.

*The heart rate* was studied in nine patients, four of whom showed little or no improvement following the operation, and five of whom showed varying degrees of benefit (Table III). During the prolonged exertion that was made possible in the latter five patients the heart rate increased as much as, or more than, it did before operation (Fig. 4). With this increased exertion the total number of beats per minute during exercise was greater than before operation in three individuals, and smaller in two. In both of the latter cases the heart rate at rest was lower after operation than preoperatively.

The amount of exercise which induced angina preoperatively caused the same increase in heart rate both before and after operation in five patients, three of whom were improved by the operation and two of whom showed no improvement. In two patients, one of whom showed clinical improvement, this amount of work caused a greater increase after operation, and in two patients, one of whom was improved (Fig. 4), the increase in heart rate was less postoperatively. The degree of clinical improvement, therefore, was unrelated to the response of the heart rate during exertion.

*The systolic blood pressure* after total thyroidectomy was studied in all eleven patients (Table III). Comparable amounts of exercise did not cause as great a rise in blood pressure after operation as preoperatively (Table III, Fig. 4). Prolonged exertion in the seven patients who showed clinical improvement was accompanied by the same or a

TABLE III

CASE NO.	TIME OF TEST	BASAL METABOLIC RATE (%)	DURING REST HEART RATE (BEATS PER MIN.)	DURING EXERCISE HEART RATE (BEATS PER MIN.)	DURATION OF EXERCISE (MINUTES)	HEART RATE (BEATS PER MIN.)	SYSTOLIC BLOOD PRESSURE (MM. HG)	EXERCISE TOL-ERANCE (MIN.)	REMARKS
5	Before operation	-14	86	142	1.4	146	150		Anginal attack
	After operation	-36	76	132	2.5	180	202		Anginal attack
10	Before operation	-24	84	160	1.8	160	142		Anginal attack
	After operation	-30	112	152	3.2	120	124		Anginal attack
24	Before operation	-17	104	144	3.0	146	128		Anginal attack
	After operation	-37	80	144	4.0	158	152		Anginal attack
25	Before operation	?	80	132	3.3	108	126		Anginal attack
	After operation	-46	68	116	3.5	116	126		Anginal attack
32	Before operation	+ 5	92	152	4.0	170	132		Anginal attack
	After operation	- 5*	80	144	5.5	168	168		No angina
27	Before operation	-19	64	92	3.5	174	136	6.7	Anginal attack
	After operation	-33	60	120	3.5	200	220		No angina
12	Before operation	+ 3	124	168	2.3	180	158	7.8	Anginal attack
	After operation	- 3*	112	144	2.5	174	172		No angina
3	Before operation	- 7			1.3	80	112	3.9	Anginal attack
	After operation	-34			1.5	144	172		No angina
17	Before operation	-15	64	112	2.5	160	164	19.5	Anginal attack
	After operation	-29	56	104	2.5	140	146		No angina
30	Before operation	- 4	104		3.8	190	148	10.0	Anginal attack
	After operation	-18	86		4.0	216	148		No angina
33	Before operation	- 7	92	148	4.0	222	214		Anginal attack
	After operation	-29	100	156	4.0	206	210	20.0	No angina

\*These patients had blood serum cholesterol of 300 mg. or more or other evidences of clinical myxedema.

greater increase in blood pressure and the same or a definitely higher level of systolic blood pressure, but no precordial discomfort. With the cessation of exercise several patients showed a further increase in systolic pressure similar to that which they showed before operation and similar to that which occurred in patients with no heart disease.

Adrenalin, like exercise, causes an increase in blood pressure and heart rate. The response to intravenous injection of adrenalin before and after total thyroidectomy has been the subject of a previous communication.<sup>28</sup> In four patients of the present series both the response to adrenalin and the response to exercise were studied.

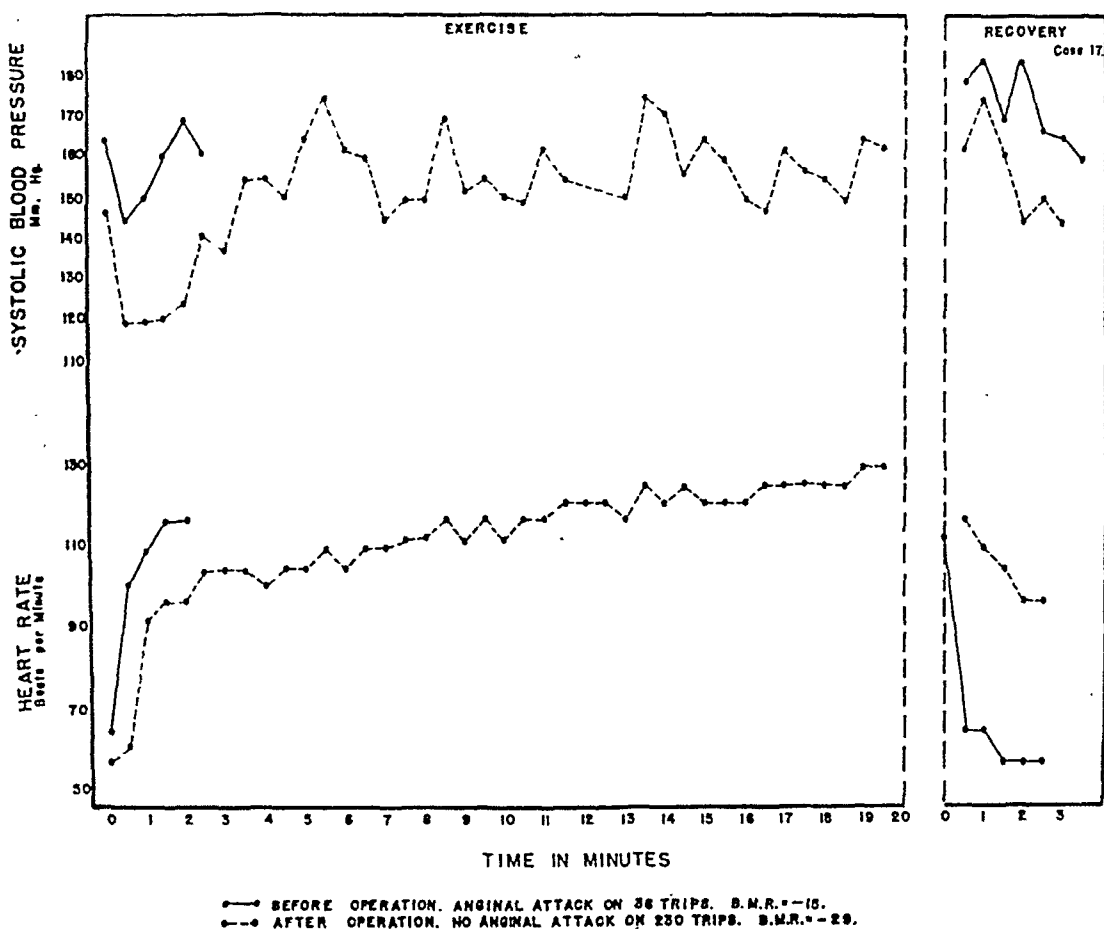


Fig. 4.—Changes in heart rate and blood pressure during exercise before and after total thyroidectomy. The duration of time between the last measurement made during exercise and the first measurement during recovery was 30 seconds or less.

The preoperative basal metabolic rate in Case 17 was -15 per cent and thirty-six trips over the staircase induced angina (Fig. 5). One week following operation, before the basal metabolism was lowered, forty-two trips failed to induce cardiac pain. This early relief of pain is due to interruption of afferent nerve pathways at the time of operation and is a temporary phenomenon.<sup>30</sup> In this patient the basal metabolic rate was maintained at the preoperative level by the administration of thyroid extract for three weeks, at which time thirty-six trips again induced angina. Thyroid extract was then omitted. Eight weeks after opera-

tion the basal metabolism was -29 per cent, and the patient had improved so that he was free of pain even after two hundred trips. The response of the blood pressure and heart rate to adrenalin and to thirty-six trips of exercise was essentially the same as before operation. Continuation of the exercise, however (two hundred trips), caused a sharp rise in blood pressure and a further increase in heart rate. At a later date (twelve weeks after operation) severe myxedema developed. At this time there was a marked decrease in the sensitivity to adrenalin, for relatively large doses (3.5 c.c. per minute of 1:100,000 solution) were required to induce the same change in blood pressure and heart rate as had previously been produced by much smaller doses (1.0 c.c. to 1.4 c.c. per minute of a 1:100,000 solution). The response of the heart rate and blood pressure, however, was essentially unchanged. Similar results were observed in the other three patients.

#### COMMENT

The lack of knowledge regarding circulatory changes associated with attacks of angina pectoris is largely due to the fact that the attacks are brief, and supervene without giving sufficient warning to allow preparation for careful, adequate study. Although several investigators have had the opportunity to measure the heart rate or blood pressure while the pain still persisted, such opportunities are rare and are largely beyond control. The lapse of time from the onset of the attack to the time when measurements can be made necessarily varies in different instances, and the normal heart rate and blood pressure for comparison must necessarily be determined at a subsequent time or from records of previous examinations. Such measurements give little information as to the behavior of the circulation at the very onset or immediately preceding the attacks when changes in the circulation might possibly be of importance in inducing the paroxysm. The rapid development, relatively short duration, and rapid disappearance of the paroxysms of pain suggest that there may be an equally rapid progression of changes in the circulation, and a single determination of the heart rate or blood pressure, therefore, fails to give an adequate picture of the circulatory changes accompanying the various phases of the attack.

Attacks of angina pectoris have been induced experimentally by adrenalin,<sup>16, 18</sup> anoxemia,<sup>17, 29</sup> and exercise.<sup>3, 25, 26, 27, 31, 32, 36</sup> The ability to induce attacks of angina at will enables one to prepare for careful observation and to observe the entire chain of events during the development, duration, and disappearance of the pain. The significance of such measurements in relation to attacks of angina pectoris as they occur clinically depends largely on how closely the induced attacks correspond to spontaneous attacks, both in clinical characteristics and in etiology. While the precipitation of attacks of angina pectoris by adrenalin or anoxemia has no close clinical counterpart, the induction of attacks by

exertion is natural and in fact is one of the characteristic clinical features. The standardized exercise tolerance test previously described<sup>27</sup> duplicates faithfully the conditions under which many attacks are precipitated in normal life. By means of this test it is possible to induce paroxysms of angina in the vast majority of patients suffering from this condition, and the clinical characteristics of the attacks so induced are identical with those usually experienced by the patient in daily life. The ability to induce typical attacks of angina under these controlled conditions makes it possible to measure accurately the heart rate and blood pressure before the attack, during the development and onset of the paroxysm, during the height of the pain, and during the recovery from the attack. The necessity for rapidly repeated measurements is clear when one observes the swift succession of changes in the circulation which take place during the precipitation and recovery from attacks of angina. Striking changes in heart rate and blood pressure are evident within a few seconds after the cessation of exercise; observations made "during the attack," therefore, give little insight into the situation at the onset or immediately preceding the paroxysm.

*Observations of the systolic blood pressure and heart rate before, during, and after paroxysms of angina pectoris, induced by exercise, reveal no characteristic changes which might aid in establishing the diagnosis.* Bischoff,<sup>3</sup> Wasserman,<sup>31</sup> Portocalis and Flora,<sup>25</sup> Wood and Wolferth,<sup>36</sup> and Wayne and Laplace<sup>32</sup> have induced attacks of angina by means of effort and measured the heart rate and blood pressure "during the attack" within a few moments after cessation of the exertion. Under such conditions the heart rate and the blood pressure were elevated in most, although not in all, patients.<sup>36</sup>

The elevation of blood pressure under such conditions is a normal reaction which takes place during the first few minutes of recovery from exercise and is a result of the exercise, not of the angina. A similar rise in blood pressure following exercise has been observed in a group of normal patients studied by Cotton, Rapport, and Lewis<sup>9</sup>; our control group, with no evidence of heart disease, showed this same reaction; a similar response was observed in the group treated by thyroidectomy who no longer developed pain on exertion; and a similar reaction was seen in patients with angina pectoris who stopped exercise before the attack was precipitated.

An entirely different picture is seen if the measurements are made at the time of onset of the anginal attack or immediately before the onset of pain; the systolic blood pressure at this time is higher in some patients, lower in others, while in still others the blood pressure is essentially the same as it was during rest (Table II).

The heart rate at the onset of attacks of angina induced by exertion is elevated, as might be expected from the nature of the stimulus employed in inducing the pain. The degree of elevation is of no aid in



establishing the diagnosis, for it varies in different patients regardless of the presence or absence of angina pectoris.

*The attacks of angina pectoris are not induced by any characteristic changes in systolic blood pressure or heart rate.* Observations of the blood pressure during paroxysms which develop spontaneously with the patient at rest reveal little agreement as to the changes in blood pressure under such conditions. Hunter,<sup>15</sup> Burgess,<sup>8</sup> and Levine and Ernstene<sup>19</sup> have found the blood pressure higher during attacks of angina than at other times. Levine and Ernstene suggest "that a temporary elevation in blood pressure is an important factor in the production of anginal attacks and may even be a necessary immediate cause of the attack."<sup>19</sup> Allbutt<sup>1</sup> cites two cases with elevated blood pressure and one with depressed blood pressure during attacks. Mackenzie<sup>22</sup> and Lewis<sup>21</sup> have presented an unusual group of cases with aortic regurgitation in which attacks of angina were ushered in by a rise in systolic blood pressure. Regarding such cases, Mackenzie states, "Although I have taken blood pressure observations in cases of angina pectoris during the attack, no others have been found which show . . . the rise in pressure consistently associated with recurrence of pain."<sup>23</sup>

The observations made in the present study show that the systolic blood pressure at the onset of attacks of angina is not always elevated but may be lower or essentially the same as the blood pressure during rest. These measurements were made during attacks induced by conditions which precipitate a large proportion, if not the great majority, of attacks which occur clinically. The observations recorded, therefore, show that such paroxysms of angina are not caused by any characteristic or specific change in systolic blood pressure.

The heart rate is elevated during attacks of angina pectoris induced by exertion. The elevation in heart rate under such conditions is undoubtedly a response of the heart to the degree and character of the work involved in the exercise. Attacks of angina induced by other stimuli are not necessarily accompanied by a change in heart rate. During the course of the present investigation an opportunity presented itself to measure the pulse rate in two individuals immediately before and within a few seconds after the onset of angina induced by sudden fright while the patients were at rest. In neither instance was the attack of pain accompanied by any appreciable change in pulse rate. Measurements of the blood pressure were not feasible, for the length of time necessary to adjust the blood pressure cuff would prevent observation of any transient changes. Mackenzie<sup>23</sup> has observed that the heart rate was increased in some patients during attacks while in others the rate became slower or was unchanged. Duke<sup>11</sup> has reported a case in which the attacks, precipitated by heat, were unaccompanied by any change in heart rate. Electrocardiograms taken by Levy,<sup>20</sup> Parkinson and Bedford,<sup>24</sup> and Brow and Holman<sup>6</sup> show the heart rate during

paroxysms of angina to be essentially the same as when the patient was free from pain, while the case reported by Gallavardin and Rougier<sup>14</sup> showed a distinct slowing during the attack. Feil and Siegel<sup>13</sup> have presented electrocardiographic tracings taken during attacks showing in some instances a definite increase in heart rate and in others an increase of less than 10 beats per minute. The tracings presented by Bousfield<sup>4</sup> show a similar slight increase in rate.

Wayne and Laplace<sup>32</sup> found a close correlation between the duration of attacks of angina induced by exertion and the length of time necessary for the heart rate to return to the resting rate. This was true in some of the cases included in the present study, but it was not true of all cases; in several instances the pain continued even after the heart rate had returned to the resting level.

Proger, Minnich, and Magendantz<sup>26</sup> noted that angina pectoris on exertion was associated in some patients with a failure of the heart rate to increase normally during exercise while in others extrasystoles developed shortly before the onset of pain. Similar reactions were noted in several of the patients studied in the present series. Since identical reactions were observed in patients without heart disease who did not develop pain on similar exertion and since angina pectoris was experienced by many patients who showed a normal cardiac response during exercise, these reactions in themselves cannot be held responsible for the attacks of pain.

The balance of evidence at the present time suggests that paroxysms of angina are induced by anoxemia or relative anoxemia of the heart muscle brought about by the inability of the coronary circulation to supply sufficient blood for the demands of the myocardium. The factors which influence the flow of blood through the coronary vessels are inadequately understood, but of undoubted importance are the caliber and rigidity of the vessels, the duration of systole and diastole, and the head of pressure at the mouths of the coronary arteries. Similarly, the demands of the myocardium are influenced by several factors including the frequency of contraction, the volume output, the velocity imparted to the blood stream, and the arterial pressure which the heart must maintain and work against.

Both the work of the heart and the coronary blood flow are influenced in part by the heart rate and the blood pressure. An increase in heart rate and systolic blood pressure increases the work which must be done by the heart, but at the same time these changes bring about an increase in coronary blood flow; whether the balance in a given instance enhances myocardial anoxemia or favors adequate myocardial nutrition cannot be prognosticated with certainty. Under certain conditions the rôle played by these two factors may be of major importance in causing a discrepancy between the supply and the demand. During episodes of paroxysmal rapid heart action, for example, the frequency and at times

irregularity of the cardiac contractions undoubtedly increase the energy expenditure of the heart muscle and at the same time probably decrease the flow of blood through the coronary vessels; it is not surprising that paroxysms of angina have been observed during such at-

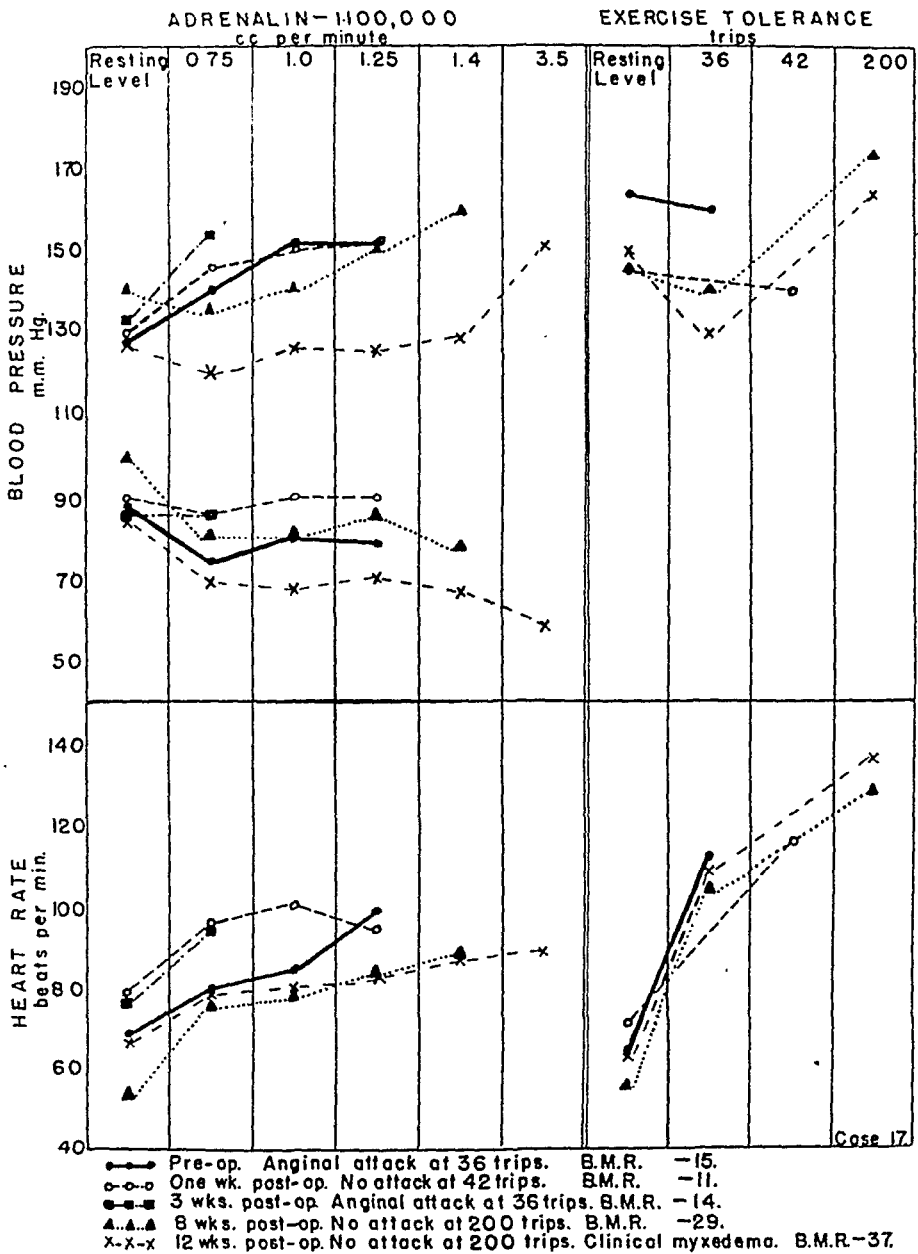


Fig. 5.—Response of the heart rate and blood pressure to exercise and to intravenously injected adrenalin both before operation and after total thyroidectomy when various degrees of clinical improvement were evident.

tacks.<sup>7, 34, 35</sup> Similarly an increase in heart rate and systolic blood pressure in a patient with aortic regurgitation is likely to be accompanied by heart pain, for the low diastolic pressure prevents adequate filling of the coronary vessels. These situations, however, are unusual in the majority of attacks which occur clinically; other factors, such as the

inadequate flow of blood through rigid or spastic coronary vessels and the increased requirements of the heart during exercise, are of major importance.

*The clinical improvement, in patients with chronic congestive failure or angina pectoris, following total thyroidectomy, is apparently independent of changes in sensitivity to adrenalin or changes in the amount of adrenalin secreted by the body.* It has been suggested that a change in sensitivity to adrenalin<sup>5, 10, 12</sup> or a decreased response of the heart to stimuli such as adrenalin or exercise<sup>30</sup> is responsible for the clinical improvement which follows total thyroidectomy.

In a previous investigation<sup>28</sup> the sensitivity to adrenalin was measured by studying the changes in blood pressure, heart rate, respiration, and oxygen consumption produced in man by known doses of adrenalin administered continuously by the intravenous route. The sensitivity to adrenalin measured by these criteria was the same before operation and after total thyroidectomy when clinical improvement was manifest. (Fig. 5.)

Although there was no change in sensitivity to adrenalin at the levels of hypometabolism maintained in these patients following total thyroidectomy, it is conceivable that the secretion of adrenalin is diminished, and the heart, therefore, is subjected to less intense stimuli.<sup>28</sup>

Unfortunately, quantitative tests for the determination of circulating adrenalin in man are not available. Indirect evidence regarding the concentration of circulating adrenalin can be obtained by measuring changes in heart rate and blood pressure, for tachycardia and an increase in arterial tension are characteristic physiological responses to adrenalin. If secreted adrenalin plays any part in the heart rate and systolic blood pressure changes during exertion, a diminution in adrenalin output following thyroidectomy would be evidenced by relatively less change in heart rate and systolic blood pressure during exercise. This is not the case, for during the prolonged exertion made possible by total thyroidectomy the heart rate and systolic blood pressure rise as high as, or higher than, during exercise before operation (Table III and Figs. 4 and 5).

There is, therefore, no evidence that exercise calls forth either a diminished secretion of adrenalin or a diminished response of the heart rate or blood pressure in man after total thyroidectomy. The improvement is rather to be related to a more favorable readjustment between diminished demands of the myocardium<sup>2</sup> and the available supply of blood through the coronary vessels.

#### SUMMARY

Attacks of angina pectoris were induced in thirty-five patients by exercise under standardized conditions. The systolic blood pressure and heart rate were determined at half-minute intervals during and follow-

ing such exercise. In this manner it was possible to determine the systolic blood pressure and heart rate not only during attacks of angina pectoris but also immediately before and at the very onset of the paroxysms of pain.

The systolic blood pressure at the onset of such attacks was higher in some cases, lower in others, and in many instances essentially the same as the blood pressure during rest. Measurements made shortly after the cessation of exercise, while the pain still persisted, revealed the systolic blood pressure to be higher than the resting level in most instances. These variations in blood pressure were the result of two factors: (1) the changes in blood pressure brought about by exercise and (2) the duration of the exercise before being terminated by the onset of pain.

The heart rate at the onset of the attacks was invariably increased: the degree of increase varied with the duration of exercise required to induce the attack and the curve of increase of the heart rate during exertion. Measurements made shortly after the cessation of exertion, while the pain still persisted, revealed the heart rate to be elevated but to a significantly lesser degree than at the onset of the attack.

Similar changes in systolic blood pressure and heart rate during and after exercise were observed in patients without evidence of heart disease.

Observations were made in patients before and after total ablation of the thyroid gland. With the prolonged exertion made possible by this operation, the systolic blood pressure and heart rate rose as high as or higher than it did during exercise before operation.

The wide variation in systolic blood pressure and heart rate at the onset of attacks of angina indicates that such changes are not primary etiological factors in their precipitation and are of no value in diagnosis.

There was no evidence that the clinical improvement following total thyroidectomy was due to a lessened increase in heart rate or systolic blood pressure or to a decreased output of adrenalin during exertion.

#### REFERENCES

1. Allbutt, Sir Clifford: *Diseases of the Arteries Including Angina Pectoris*, London 2: 256, 1915.
2. Altschule, M. D., and Volk, M. C.: The Minute Volume Output and the Work of the Heart in Hypothyroidism, *J. Clin. Investigation* 14: 385, 1935.
3. Bischoff: Ischaemia Cordis Intermitens (Angina pectoris durch Anstrengung), *Schweiz. med. Wchnschr.* 57: 218, 1927.
4. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysms, *Lancet* 2: 457, 1918.
5. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* 52: 165, 1933.
6. Brow, G. R., and Hohman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, *AM. HEART J.* 9: 259, 1933.
7. Burak, M., and Scherf, D.: Angina pectoris und paroxysmale Tachykardie, *Wien. Arch. f. inn. Med.* 23: 475, 1933.
8. Burgess, A. M.: Reaction to Nitrites in Anginal Syndrome and Arterial Hypertension, *Ann. Int. Med.* 5: 441, 1931.

9. Cotton, T. F., Rapport, D. L., and Lewis, T.: After Effects of Exercise on Pulse Rate and Systolic Blood Pressure in Cases of "Irritable Heart," *Heart* 6: 269, 1915.
10. Cutler, E. C., and Schnitker, M. T.: Total Thyroidectomy for Angina Pectoris, *Ann. Surgery* 100: 578, 1934.
11. Duke, W. W.: Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Functional Cardiac Disorders Including Angina Pectoris, Tachycardia, and Ventricular Extrasystoles, *J. Allergy* 4: 38, 1932.
12. Eppinger, E. C., and Levine, S. A.: Effect of Total Thyroidectomy on Response to Adrenalin, *Proc. Soc. Exper. Biol. & Med.* 31: 485, 1934.
13. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
14. Gallavardin, L., and Rougier, Z.: Accès d'angine de poitrine avec hypotension artérielle. Extrême et accidents nerveux syncopaux et épileptiformes, *Paris méd.* 2: 15, 1928.
15. Hunter, W. K.: Discussion on Angina Pectoris, *Brit. M. J.* 2: 1128, 1909.
16. Katz, L. M., Hamburger, W. W., and Lev, W.: Diagnostic Value of Epinephrine in Angina Pectoris, *AM. HEART J.* 7: 371, 1932.
17. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects: Its Bearing on the Mechanism of Attacks of Angina Pectoris, *AM. HEART J.* 9: 771, 1934.
18. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: Use of Epinephrine as a Diagnostic Test for Angina Pectoris, *Arch. Int. Med.* 45: 191, 1930.
19. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attacks of Angina Pectoris, *AM. HEART J.* 8: 323, 1933.
20. Levy, J. R.: Valeur semeiologique des alterations du complexe ventriculaire électrique dans les syndromes angineux, *Arch. d. mal. du Cœur* 22: 523, 1929.
21. Lewis, T.: Angina Pectoris Associated With High Blood Pressure and Its Relief by Amyl Nitrite: With a Note on Nothnagel's Syndrome, *Heart* 15: 305, 1931.
22. Mackenzie, J.: A Case of Angina Pectoris Associated With Great Excitability of the Vaso-constrictor Mechanism, *Heart* 2: 265, 1911.
23. Mackenzie, Sir James: Angina Pectoris, London, 1923, Oxford Medical Pub.
24. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, *Lancet* 1: 15, 1931.
25. Portocalis, A., and Flora, G. T.: Angine de poitrine d'effort avec érythème initial et poussée hypertensive. *Bull et mém. Soc. méd. d. hôp. de Paris* 47: 1650, 1931.
26. Proger, S. H., Minnich, W. R., and Magendantz, H.: Circulatory Response to Exercise in Patients With Angina Pectoris, *AM. HEART J.* 10: 511, 1935.
27. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients With Angina Pectoris on Exertion, *Am. J. M. Sc.* 188: 646, 1934.
28. Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L.: Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland: XVI. The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, *Arch. Int. Med.* 56: 38, 1935.
29. Rothschild, M. A., and Kissin, M.: Production of Angina Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.
30. Sawyer, M. E. M., and Brown, M. G.: Effect of Thyroidectomy and Thyroxine on the Response of the Denervated Heart to Injected and Secreted Adrenine, *Am. J. Physiol.* 110: 620, 1935.
31. Wasserman, S.: Die Angina pectoris, ihre Pathogenese und Pathophysiologie, *Wien. klin. Wchnschr.* 41: 1514, 1928.
32. Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort, *Clin. Sc.* 1: 103, 1933.
33. Weinstein, A. A., Davis, D., Berlin, D. D., Blumgart, H. L.: Mechanism of the Early Relief of Pain in Patients With Angina Pectoris and Congestive Failure After Total Ablation of the Normal Thyroid Gland, *Am. J. M. Sc.* 187: 753, 1934.
34. White, P. D., and Camp, P. D.: Status Anginosus Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia, *AM. HEART J.* 7: 581, 1932.
35. Wolff, L.: Angina Pectoris (or Status Anginosus) and Cardiac Asthma Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia, *New Eng. J. Med.* 208: 1194, 1933.
36. Wood, F. C., and Wolferth, C. C.: Angina Pectoris, *Arch. Int. Med.* 47: 339, 1931.

# LIGATION OF THE CORONARY ARTERIES IN JAVANESE MONKEYS\*

## II. ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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IN PART I<sup>1</sup> we described the changes in the ventricular electrogram which supervened after ligation of the ramus descendens anterior (L) in seventeen monkeys (*Macaca irus*) and of the right artery (R) in fourteen of these animals. In one monkey the right artery was obstructed seven weeks after left ligation.

The following discussion concerns the arrhythmias which were observed in these monkeys, whether they were accompanied by conduction disturbances or not. They include extrasystoles, paroxysmal tachycardia, ventricular fibrillation, sino-auricular block, auriculoventricular block, bundle-branch block, and nodal rhythm.

It should be noted at once that no case of flutter or fibrillation of the auricles was observed. It is possible that this is due to the fact that the arteries were ligated too far from the aorta to include with certainty any possibly existing rami cristae terminales or rami atriales. Lesions of the auricles were not found morphologically.

### EXTRASYSTOLES

To localize the point of origin of ectopic beats by means of the electrocardiogram, the only method available, in our experience it is necessary to make simultaneous records of at least two and preferably all three of the standard leads. It can happen, for instance, that in Lead I a ventricular complex is seen without any preceding P-wave, while in Leads II and III P-waves, both negative and of the same size, prove to be present (See Fig. 1, segment B). If recording had been made successively and not simultaneously, the latter complexes would probably have been assigned to another point of origin.

Moreover, in successive registration it is never known with certainty whether the extrasystoles caught in the different leads really represent the same type—in other words, whether they had a common point of origin.

For such reasons we have, especially when studying extrasystoles, always had great success with the use of simultaneous recording and have met with difficulties whenever the records were made successively.

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An experimental study made by one of us,\* which was begun at about the time we started the coronary ligations and will be published separately, put in our hands the various types of electrocardiogram appearing in the three simultaneous leads when the *Macaca* heart is stimulated by induction shocks at various places, the thorax being closed, the animal respiring spontaneously. On the basis of these results, which in general agree with those recently published by Kountz and his associates,<sup>2</sup> we were usually able to determine from our curves the point of origin of the extrasystoles observed in our coronary monkeys.

First and foremost let it be emphasized that we never found any irregularity in the heart action of monkeys before operation. In the past years we have examined over 300 monkeys and have never found one with a spontaneous extrasystole. Our experience is that these "spontaneous" extrasystoles in various experimental animals, and certainly in monkeys,

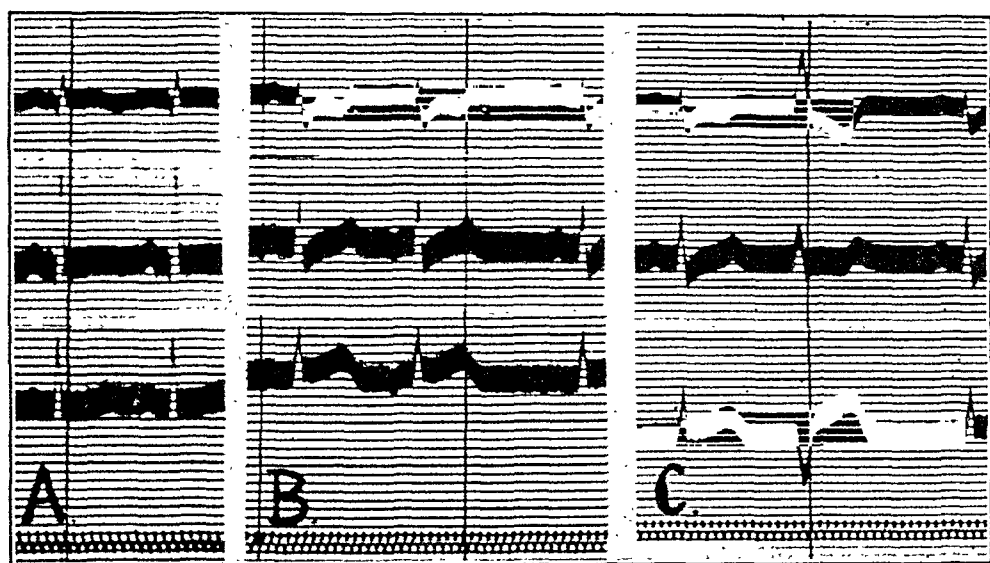


Fig. 1.—Monkey 37 R. *A*, before operation; *B*, 15 min., *C*, 17 min. after ligation of right artery. Second complex in *B* shows auricular extrasystole without P in Lead I, but with negative P in Leads II and III. Second complex in *C* ventricular extrasystole from right apex, interfering with P-wave.

occur less frequently than in man, which is perhaps of some interest to the clinician. Nor did we ever see extrasystoles develop in a monkey under the influence of "emotion" or under the influence of the narcosis as applied in our experiments.<sup>3</sup> We are convinced, therefore, that the extrasystoles described here may be regarded as resulting from the coronary ligations.

They may, then, be unspecific (i.e., due to the operative trauma as such), or specific (i.e., due to the changes produced in the heart by the coronary obstruction as such), formerly called by Lewis<sup>4</sup> a local state of irritability in the area of the anemic heart wall.

First, as regards the influence of the operative trauma, which as a rule is not considered of importance:<sup>5-7</sup> it is our experience that extensive operations in the monkey thorax (for instance, the entire operation already described without coronary ligation but including the passage of

\*Storm.



a ligature through the superficial layers of the heart muscle, or the exposure of the heart and subsequent incision and section of parts of the conduction system) usually may be done without inducing extrasystoles. Also such operations are in our experience not followed by ectopic beats. Since about 60 per cent of our monkeys after coronary ligation showed no extrasystoles, it is our opinion that no great etiological significance need be attached to possible mechanical irritation by the ligature itself. Moreover, it might be expected that any postoperative extrasystoles which did arise as a result of such direct irritation would originate at the site of the ligature. To what extent such extrasystoles probably ap-

TABLE I  
NUMBER AND TYPE OF EXTRASYSTOLES OBSERVED AFTER LIGATION

MONKEY	FIRST E. S. OBSERVED AFTER LIGATION	LAST E. S. OBSERVED AFTER LIGATION	SURVIVAL AFTER OPERATION	NUMBER AND TYPE OF E. S.
4 L	48 min.	63 min.	6 mo.	1 nodal 5 base <sup>*</sup> 7 left <sup>*</sup>
5 L	20 min.	20 min.	36 min.	1 right <sup>*</sup> 1 nodal 1 left <sup>*</sup>
6 L	1 wk.	1 wk.	7 wk.	1 apex <sup>*</sup>
6 L + R	65 min.	65 min.	4 hr.	3 auricular
13 L	10 min.	10 min.	23 min.	1 left apex
16 L	7 min.	7 min.	13 min.	1 nodal or apex†
19 L	4 days	4 days	2 mo.	1 base <sup>*</sup>
10 R	5 hr.	3 mo.	6 mo.	336 right apex and 48 left apex
12 R	1 day	12 days	5½ mo.	313 right apex and middle
14 R	4 min.	8 min.	4 mo.	2 right base
36 R	22 min.	22 min.	6 hr.	3 right apex
37 R	15 min.	18 min.	1 hr.	1 auricular and 1 right apex

\*Not to be localized more exactly because seen in only one lead.

†Not to be localized more exactly because complicated by bundle-branch block.

peared in our experiments will be discussed after we have first presented in Tables I and II a review of the extrasystoles recorded after coronary ligation.

Records were made several times per hour in the first two or three hours after the operation, the projection of the strings being carefully watched in the intervals. When the monkey survived for a longer period, curves were taken about twice a week. Each record contained about 20 cardiac cycles in each lead, taken simultaneously or successively. It was, of course, practically impossible to leave the animals continually connected to the galvanometers. It is certain, therefore, that although about 1,200 curves were made, there have been more extrasystoles among our material than could be collected for our tables.

Some of the curves with extrasystoles after ligation are reproduced in this paper; one was shown in Fig. 14, Part I.

TABLE II

RELATION BETWEEN TYPE OF EXTRASYSTOLE AND TYPE OF LIGATION

	LEFT LIGATION	RIGHT LIGATION
Total number of monkeys	17	15
Total number showing extrasystoles	6	6
Among these showed:		
Auricular E. S.	0	2
Nodal E. S.	2	0
Left ventricular E. S.	3	1
Right ventricular E. S.	1	5
Left base E. S.	0	0
Left apex E. S.	1	1
Right base E. S.	0	1
Right apex E. S.	0	4
Undetermined	5	0

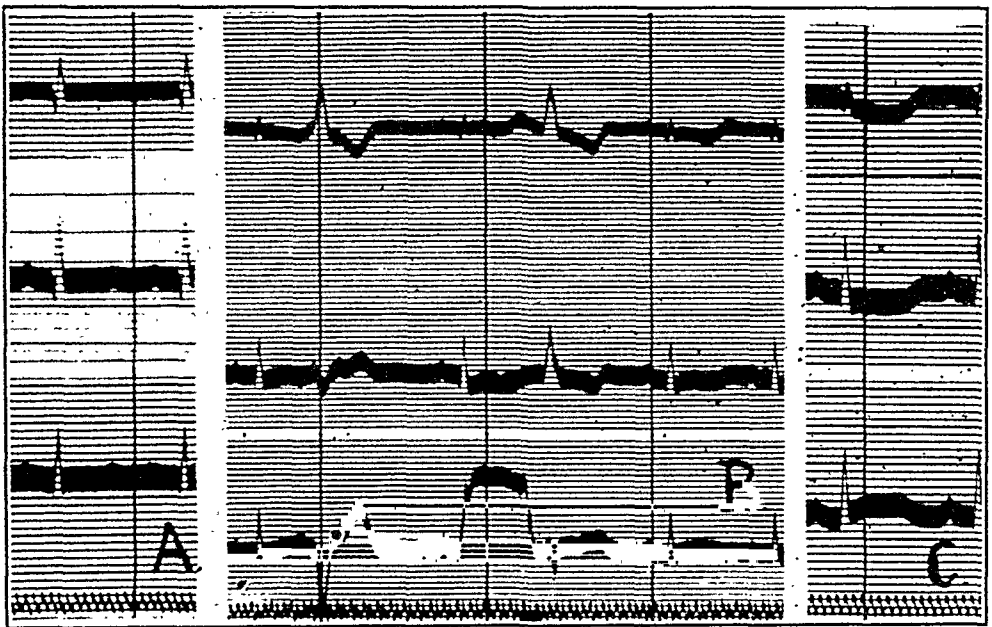


Fig. 2.—Monkey 36 R. A. before operation; B, 22 min., C, 52 min. after ligation of right artery. In B second complex extrasystole from right ventricular apex, fourth complex point of origin a little higher, but still in apical part. In B Lead III calibration deflection just before second extrasystole.

In spite of the fact mentioned above, that we do not attribute any dominant significance to local irritation caused by the ligature and practically none to operative trauma, we will not entirely exclude the former as a possible cause of a part of our extrasystoles. We regard such local irritation as a possible cause of the nodal and basal extrasystoles of Monkeys 4 L, 5 L, and 14 R, for they all originated in or near the place of ligation, appeared shortly after the operation, and were not seen again in subsequent records. The same holds good for the auricular extrasystole of Monkey 37 R (Fig. 1 B), in which animal the ligature was found by microscopic examination to have included also a small part of the right auricle.

On the other hand, we are of the opinion that the extrasystoles originating in the apical part of the ventricles (as in Fig. 2) could not arise

from local irritation of the ligatures and must therefore be regarded as specific results of the internal changes developed in or near the muscle area formerly supplied by the ligated vessel.

In particular, Monkeys 10 R and 12 R point to the possibility that such extrasystoles, especially if they show a tendency to persist for a

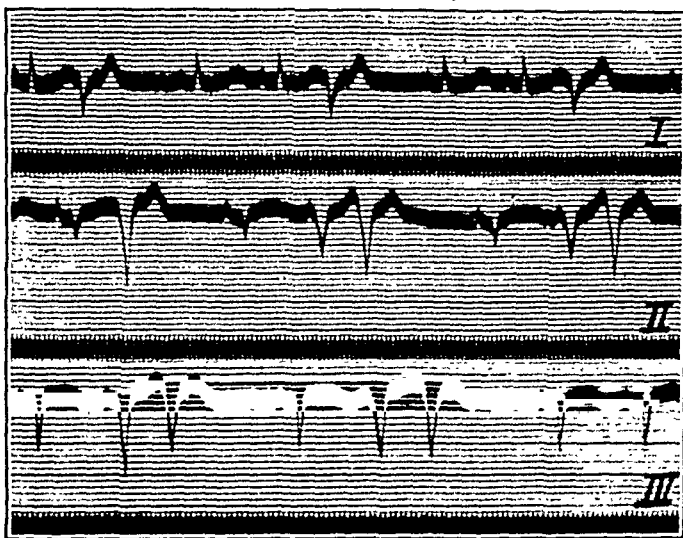


Fig. 3.—Monkey 10 R. Isolated and coupled extrasystoles, originating in left apex, six days after ligation of right artery. This was seen only once in this animal; the other extrasystoles preceding and following the paroxysm were of the right apex type. See also Fig. 5 A.

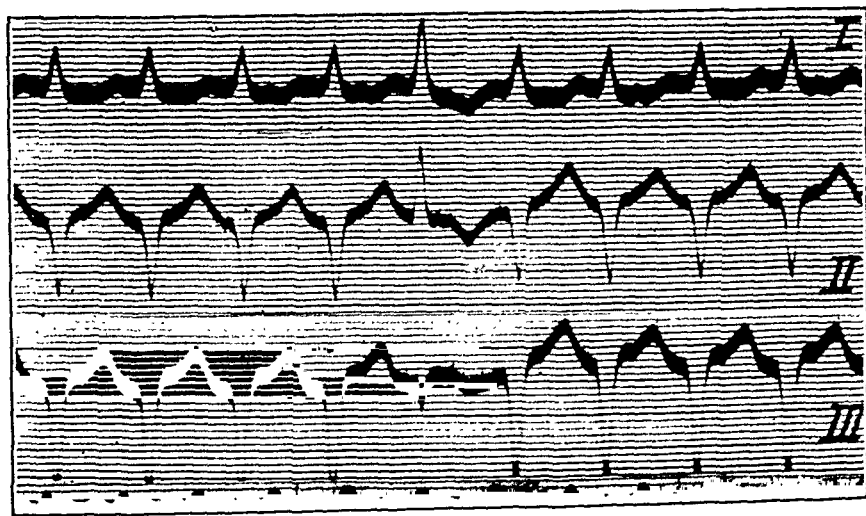


Fig. 4.—Monkey 10 R. Paroxysm of ventricular tachycardia, one week after ligation of right artery, originating in right apex, the fifth complex in right apex somewhat higher.

long time and to develop into paroxysms of ventricular tachycardia, can bear a more or less localizing character.

Repeating this investigation with a larger number of monkeys and with still more frequent electrocardiographic recordings would probably place this opinion, which is also found in the literature,<sup>8-14</sup> on a more certain basis.

## PAROXYSMAL TACHYCARDIA

In Monkeys 10 R and 12 R we observed salvos of extrasystoles, starting and ending as isolated or coupled ectopic ventricular beats of the same type as seen in the paroxysm.

The increase in heart rate during these attacks is in monkeys not as large as in man. This is undoubtedly connected with the fact that the normal monkey heart beats so rapidly that the normal diastole is shorter than the normal systole.<sup>3</sup>

*Monkey 10 R.*—The type of extrasystole before the paroxysms usually indicated the right apex as the point of origin, with this remarkable exception that on a given day (Fig. 3) groups of one or two extrasystoles were observed originating in the left apex.

The paroxysms on the following days (Fig. 4) and also all extrasystoles thereafter were, however, clearly of the right apex type. In connection with the septum

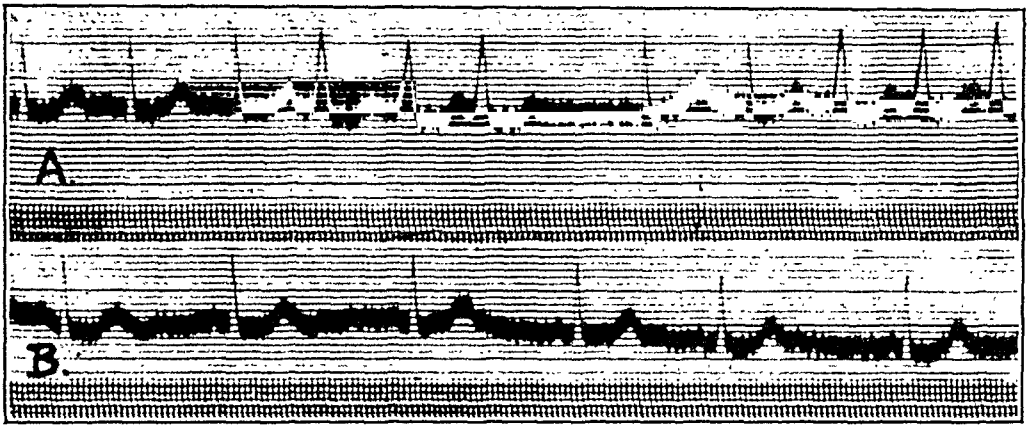


Fig. 5.—Monkey 10 R. Eight days after ligation of right artery. Lead I only. A, before; B, during bilateral pressure on region carotid sinus. Vagus reflex.

lesion, described in this animal, this temporary variability of extrasystole type appears to us in all probability to indicate a point of origin that usually was located in the right apical part of the septum but occasionally and exceptionally lay in the contiguous left apical part.

This monkey showed beforehand (Fig. 10) a prolonged P-R interval, periods of Wenckebach, and dropped beats.

A remarkable observation was made in this animal on April 28, 1933, when we succeeded, as shown in Fig. 5, eight days after the operation, in temporarily checking the paroxysm by a bilateral pressure on the region of the carotid sinus, comparable to the clinical "vagus pressure test," which in fact concerns a vagus reflex. That we were dealing here with such a reflex, as described by Hering,<sup>15</sup> and not with a casual change in the rhythm, was proved in our opinion by the fact that the frequency of the normal heartbeats, which was 180 in the intervals between the paroxysms, fell to 96 during pressure on the carotid sinus (Fig. 5 A and B). At the same time the P-R interval was shortened, indicating

probably a downward shifting of the pacemaker. Immediately the pressure was released, the paroxysms of extrasystoles returned, for a time even more violently (in groups of six or seven as against the earlier groups of three). After that day no further attacks were observed although now and then there appeared isolated extrasystoles of the right apex type; thus at the time the extrasystoles reacted to the "vagus pressure," they were already in all probability tending to disappear from other causes. Still our observation in this monkey seems conformable to those of Lewis<sup>8</sup> in the dog, in which animal paroxysms could be checked by electrical vagus stimulation in 30 per cent of his cases.

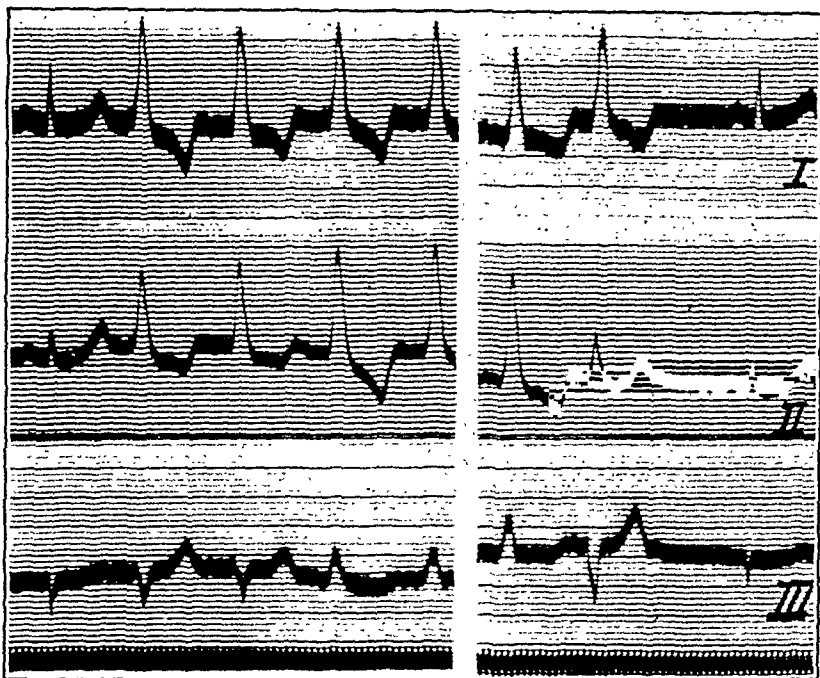


Fig. 6.—Monkey 12 R. Beginning and end of paroxysm of ventricular tachycardia, originating principally in right apex, but sometimes somewhat higher, 9 days after ligation of right artery.

Monkey 12 R showed no septum lesions. One day after the right ligation isolated extrasystoles of the right apex and right middle type appeared (Part I, Fig. 14 C), which increased to paroxysms some days later (see Fig. 6). These remained for one day only and disappeared in the course of the next four days, passing through a stage of isolated extrasystoles. If a study had been made only in Lead I, it would have been impossible in the case shown in Fig. 6 to detect the migration of the point of origin from the apex to the middle of the right ventricle and vice versa (see especially Lead III).

One would be tempted to connect the appearance of an extrasystole of other type at the end of a paroxysm (see Fig. 6) with the ending of the attack as a matter of cause and effect since it seems possible experimentally to end a paroxysm by interjecting a second circulating wave into one that is already established.<sup>16</sup> However, we observed in clinical curves as well as in our experimental ones that similar extrasystoles of

other type often do not bring such a paroxysm to an end (see Fig. 4) and, on the other hand, that quite often an attack ends without the intervention of an extrasystole of other type.

Paroxysms of ventricular extrasystoles were seen only in the two monkeys described above, in both cases after ligation of the right artery. In cats and dogs they seem to occur more frequently, also especially after right ligation.<sup>8, 10, 11</sup> Why, then, were they relatively so uncommon in our monkeys? Perhaps in this regard the following is of some importance.

The monkey heart is probably only accessible to ectopic stimuli for a very short time, owing to its relatively long systole and relatively very short diastole. A larger portion of these stimuli will threaten to occur during systole and at that period will be either incapable of producing

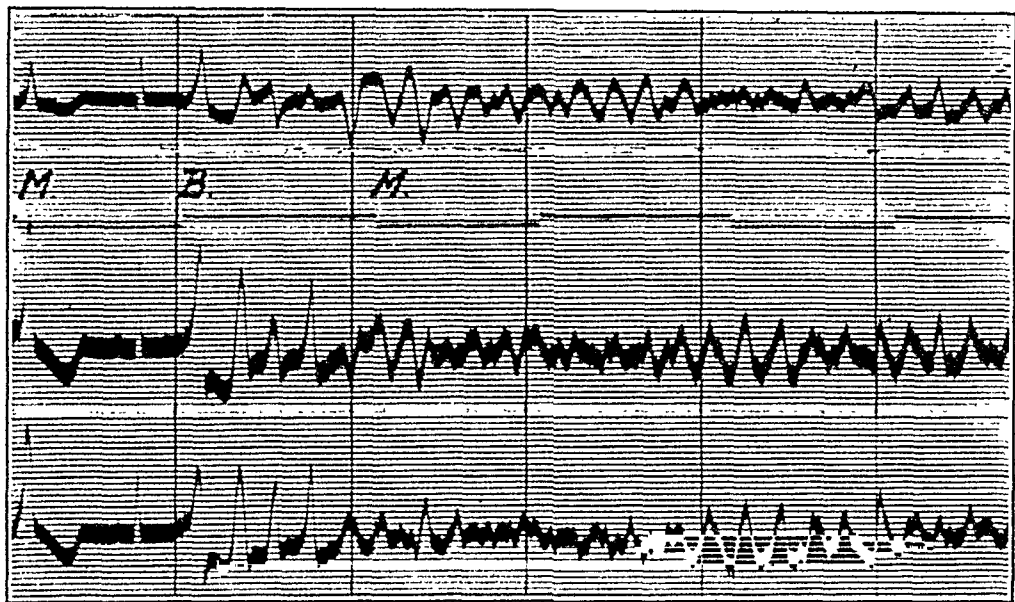


Fig. 7.—Ventricular fibrillation in *Macaca* after stimulating conus arteriosus with break shock (*B*) at end of systole. Thorax closed. Spontaneous respiration. First complex: extrasystole from conus arteriosus; second: last normal electrocardiogram during which the fatal stimulus *B* enters.

any effect or, if falling toward the end of systole, will tend to produce fibrillation.<sup>17, 18</sup> Thus the monkey heart might have a smaller chance to develop extrasystoles or paroxysms during a longer period and a greater chance to fall soon into fibrillation.

Thinking along these lines we come automatically to the study of ventricular fibrillation in our monkeys.

#### VENTRICULAR FIBRILLATION

In the course of his investigations of experimental extrasystoles mentioned above, one of us\* was able to record that actually in *Macaca* a ventricular extrasystole, provoked artificially in the latest part of a normal systole, can pass over into fibrillation (see Fig. 7).

\*Storm.

This is in accordance with the observations in frogs and dogs which have just been mentioned<sup>17, 18</sup> and also with a record Feil and his associates<sup>19</sup> made in a dog after coronary ligation.

It is therefore possible that in those of our monkeys which developed ventricular fibrillation the cause lay in one or more extrasystoles occurring just at the "fatal" moment. We did not succeed, however, in photographing this, nor could it be deduced with certainty from the observations collected in Table III.

TABLE III

REVIEW OF EXTRASYSTOLES OBSERVED IN THOSE MONKEYS WHICH DEVELOPED VENTRICULAR FIBRILLATION

MONKEY	TIME OF APPEARANCE OF VENTRICULAR FIBRILLATION AFTER OPERATION	PRECEDING EXTRA- SYSTOLES OBSERVED OR NOT	REMARKS
5 L	36 min.	Yes	Small amount of chloroform.
13 L	23 min.	Yes	
15 L	33 min.	No	
16 L	13 min.	Yes	
19 L	±2 mo.	Yes	
26 L	27 min.	No	Both vagus nerves previously cut.
49 L	5 days	No	
52 L	16 min.	No	
40 R	35 min.	No	
X R	15 min.	No	

However, in regard to Table III, it must be noticed that: (a) we never succeeded in recording the beginning of fibrillation in these monkeys, and therefore it is possible that the "fatal" extrasystole escaped us; (b) there may have been isolated extrasystoles which, in spite of our numerous recordings, also escaped us; (c) it is possible that still more monkeys died of fibrillation, as will be described later.

Nevertheless, it is certainly remarkable that just the monkeys which showed the most extrasystoles (10 R and 12 R) did not pass into fibrillation, and further that the frequency of the phenomenon seemed much greater after left ligation than after right ligation, a fact which was not observed of the extrasystoles. Of the twelve monkeys which showed extrasystoles, six after left and six after right ligation (see Tables I and II), only four, all left monkeys, went with certainty into fibrillation.

To what extent is the fibrillation we have described specifically the result of the disturbance in the coronary circulation; to what extent is it not?<sup>20</sup>

Fibrillation can for instance be caused by a mechanical stimulus falling at a "fatal" moment in the cardiac cycle, but in that case it begins immediately. We did observe this kind of fibrillation in cases of bundle-branch sections at the instant the knife cut into the ventricle, or in experiments on extrasystoles at the instant electrodes were stuck into the

heart muscle. We observed it also in Monkey 28, which was not further discussed here, in which it started at the very first attempt to ligate the left artery at the very first prick of the needle before anything was tied off. This immediate beginning is characteristic of mechanical fibrillation.

In the cases of Table III, which shows that in eight out of seventeen left monkeys and two out of fifteen right monkeys the heart went with certainty into fibrillation, in our opinion this "mechanical" fibrillation did not play any part.

Was the fibrillation caused by the narcosis or by the operative trauma?

In the course of many thoracotomies on monkeys we have never observed a case of fibrillation as long as the heart was not operated on, nor did we ever see a case induced by pernocton or evipan sodium narcosis per se. Neither the operative trauma as such nor the narcosis as such need therefore be taken into consideration here as etiological factors.

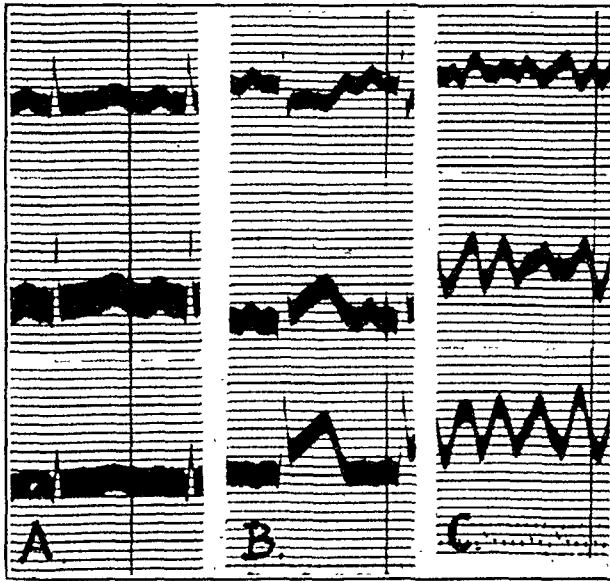


Fig. 8.—Monkey X R. A, before operation; B, 10 min., C, 15 min. after cutting both vagus nerves and ligation of right artery.

For these reasons we regard the cases of fibrillation collected in Table III as a sequel of local biological changes in the heart caused by the disturbance in the coronary circulation. In this connection it must be pointed out, however, that certainly in Monkey 19 L and probably in Monkey X R a secondary cause also played a part.

In *Monkey 19 L* two months after the operation, when the animal became restless during a registration, a very small amount of chloroform was administered by an assistant, something which had never been done before and has never been done since in our series of experiments. Fibrillation set in immediately.

In *Monkey X R* the vagi were cut on both sides before the ligation in order to observe if this procedure would affect the S-T deviation expected or would promote the appearance of extrasystoles. No noticeable influence upon the S-T deviation was found, but it is possible<sup>12</sup> that the development of fibrillation was thereby accelerated (see Fig. 8).



We have described as fibrillation only those cases which could with certainty be recognized as such, either by actually seeing the heart fibrillating or by the electrocardiographic record or by noticing the typical vibrations of the string. It is, however, not excluded that also Monkeys 17 L, 23 R, 36 R, and 41 R died in fibrillation, two days, six hours, six hours, and four days, respectively, after their operations. Among these animals only 36 R showed extrasystoles. It is true that we did not observe their fibrillation as such. In Monkey 6 L + R we believe fibrillation improbable. In Monkeys 25 R and 37 R we know for certain that the heart finally stopped beating without intervening fibrillation. These last monkeys showed a fading of the heart action, an increasing bradycardia with bizarre terminal ventricular complexes, similar to those seen in suffocation. It is probable that in these cases a primary heart insufficiency caused a failure of respiration and this finally a secondary failure of the heart due to asphyxia.<sup>21</sup>

Not only in experimental suffocation of *Macaca*, but also after the very rapid intravenous injection of large doses of pernocton or evipan sodium, which we usually give for killing an animal instantaneously, the heart stopped according to electrocardiographic control quite certainly without any fibrillation.

From the described observations on fibrillation we conclude that the chance of fibrillation after coronary ligation is relatively greatest during the first forty minutes; that if it has not developed within about five days, there is a very great probability that it will never set in; and finally that quite certainly not every death after coronary ligation is to be attributed to fibrillation.

Fibrillation once developed, or at least once observed, never stopped spontaneously. Nor could we ever succeed in stopping fibrillation by chemical or physical methods, as, for instance, described by Wiggers<sup>22</sup> and Hooker.<sup>23</sup> Without going into the theories of fibrillation, let us state that these measures did not prove effective in cases of fibrillation after coronary ligation.

#### CONDUCTION DISTURBANCES

In the experimental animals, discussed below, various conduction disturbances were observed. The origin of these disturbances must be sought in the coronary obstruction since they never appeared in monkeys to which the same methods of narcosis and operation were applied, but the coronary artery was not ligated.

*Monkey 16 L.*—One or two minutes after ligation of the anterior descending branch, an S-T deviation appeared. In this animal the leads were recorded only successively. After five minutes, while Lead I was actually being recorded (Fig. 9 C I) there appeared a disturbance of intraventricular conduction. This disturbance was characterized in Lead I by a progressively increasing downward S-wave and upward T-wave (complexes *b*) and began originally alternating with the earlier developed "normal" coronary electrocardiogram (complexes *c*). There later appeared (partly reproduced) two groups of five complexes (*b*) separated by one

complex (*e*) after which *b* became permanent; and also Leads II and III, taken in succession, proved permanently inverted (*C II* and *C III*); in both Leads II and III QRS is inverted and broadened, while in Lead III it is also clearly feathered. In both, the after-wave is high and positive.

What here develops within one minute (five minutes after ligation) can hardly be anything other than a *bundle-branch block* in this monkey, presumably a right block. It is, however, quite possible that the right block caused by section of the bundle branch in a normal monkey heart shows another form of curve, since in our case the coronary ligation might have changed the function of the ventricular muscle also peripherally to the conduction system.

Finally an extrasystole (*D II*) was seen in this animal, which thirteen minutes after the ligation developed ventricular fibrillation. This extrasystole was unfortunately observed only in Lead II. Therefore the point of origin cannot be

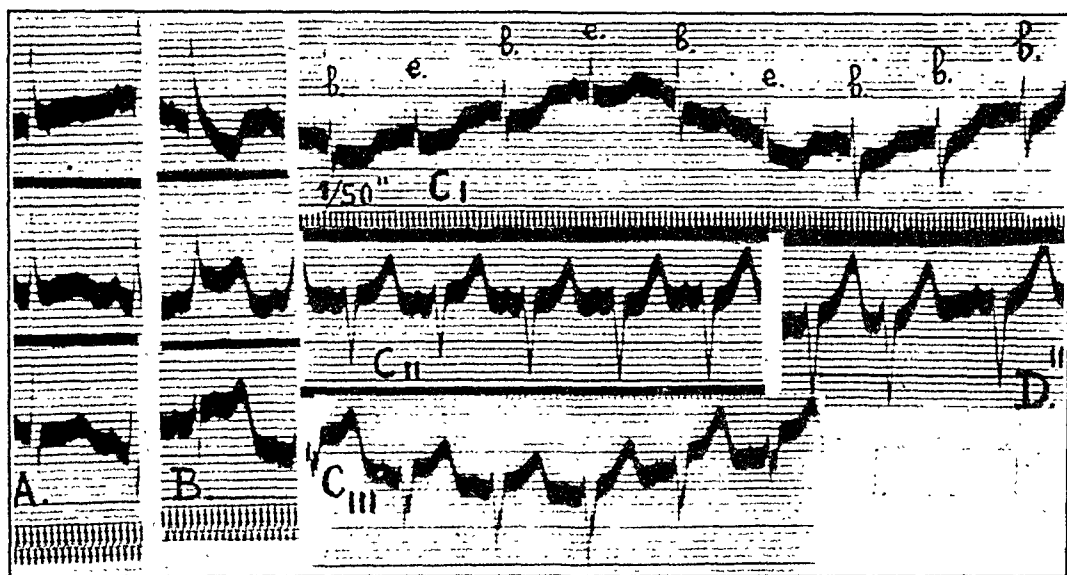


FIG. 9.—Monkey 16 L. Leads taken successively. A, before operation; B, 2 min., C, 5 min., D, (Lead II only) 7 min. after ligation of the ramus descendens anterior. In C, during Lead I developed bundle-branch block (*b*), at first alternating with normal beats (*e*), later developed in C II and III. In D II second complex extrasystole.

determined exactly, especially since the ventricular electrocardiogram has already been modified by the bundle-branch block. Was it a nodal extrasystole forced into recording an abnormal ventricular complex, or did it originate in the left or right ventricular apex, in both cases recording such a complex in a normal heart? In this instance Lead I, which is at present lacking, would have been especially useful for giving further information. It may be concluded from the curves that in this monkey very probably the septum function was disturbed although, as a result of the short survival of the animal, a lesion did not become manifest. We shall discuss later this septum involvement in connection with the direction of the S-T axis here observed ( $+99^\circ$ ).

*Monkey 10 R.*—After right ligation a definite S-T deviation appeared within about two minutes. The P-R interval before the operation was 0.07 sec. (normal in a monkey); eight minutes after the operation it was 0.10 sec.; twenty-eight minutes after the operation Wenckebach's periods and dropped beats appeared (Fig. 10)

during which P-R increased to 0.13 sec.; one hour after the ligation P-R was 0.12 sec. and the symptom of dropped beats had disappeared. This increase of the P-R interval remained for about five days, after which P-R again returned to 0.07 just

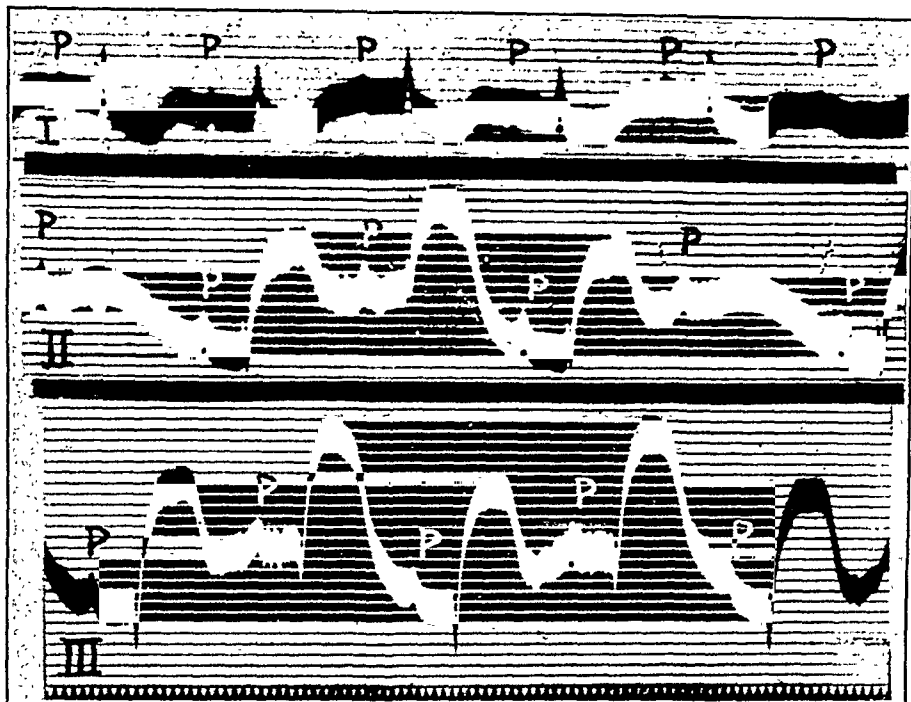


Fig. 10.—Monkey 10 R. Leads taken successively, 28 min. after ligation of right artery. Progressive lengthening of P-R interval, dropped beats. See also Part I, Fig. 7 and this paper Figs. 3, 4, and 5.

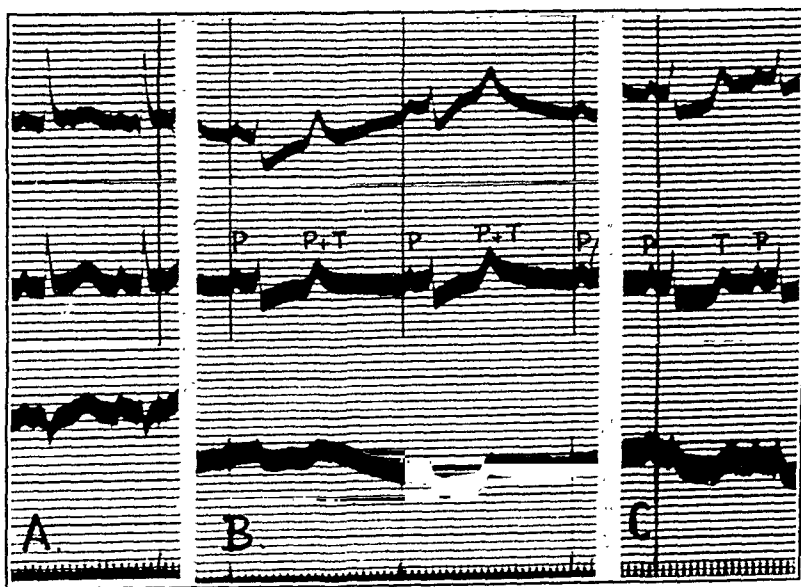


Fig. 11.—Monkey 25 R. A. before operation; B, 4 min., C, 9 min. after ligation of right artery. During B, 2 to 1 block.

about at the time the attacks of ventricular extrasystoles (see above) began to appear.

*Monkey 25 R.*—After ligation of the right artery a definite S-T deviation developed within about four minutes. Before the operation the P-R interval was 0.07 sec.

and the ventricular rate 225 per minute. Four minutes after the operation a 2 to 1 block set in with a sometimes slightly shortened P-R interval and a ventricular rate of 120 (see Fig. 11). It appears that the auriculoventricular node or bundle was still conducting quite well at this frequency of 120 per minute but that it became very easily fatigued or recovered slowly and therefore could not pass the 240 sinus

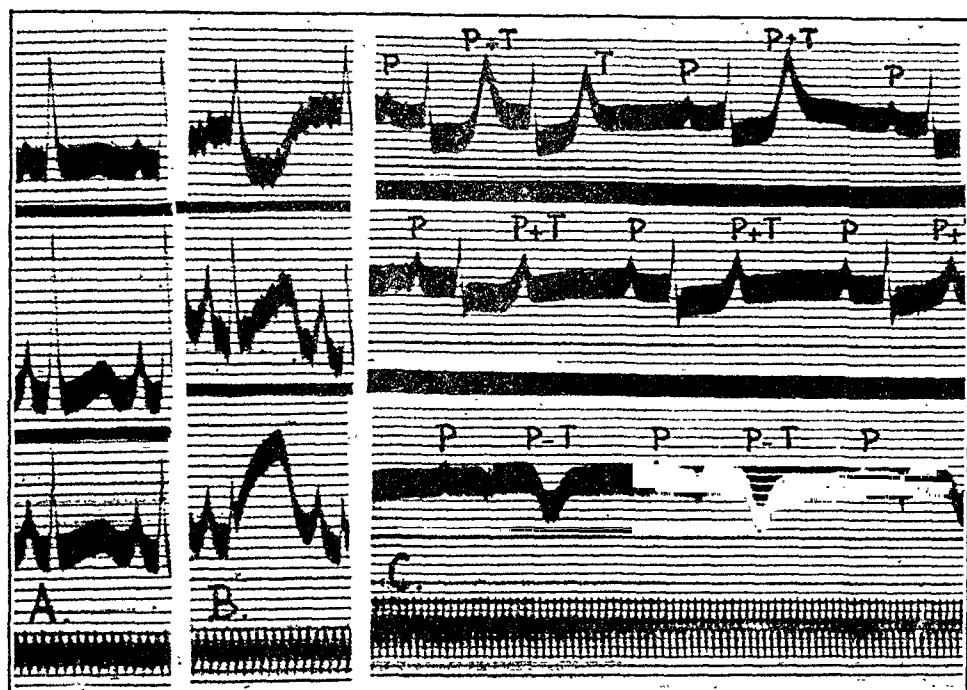


Fig. 12.—Monkey 6 L+R. A, before operation; B, 34 min. after ligation of the ramus descendens anterior on March 28, 1933. C, 1 hour after ligation of right artery on May 17, 1933. In C, 2 to 1 and 3 to 2 block, lengthened P-R interval. During Lead I sometimes sino-auricular block.

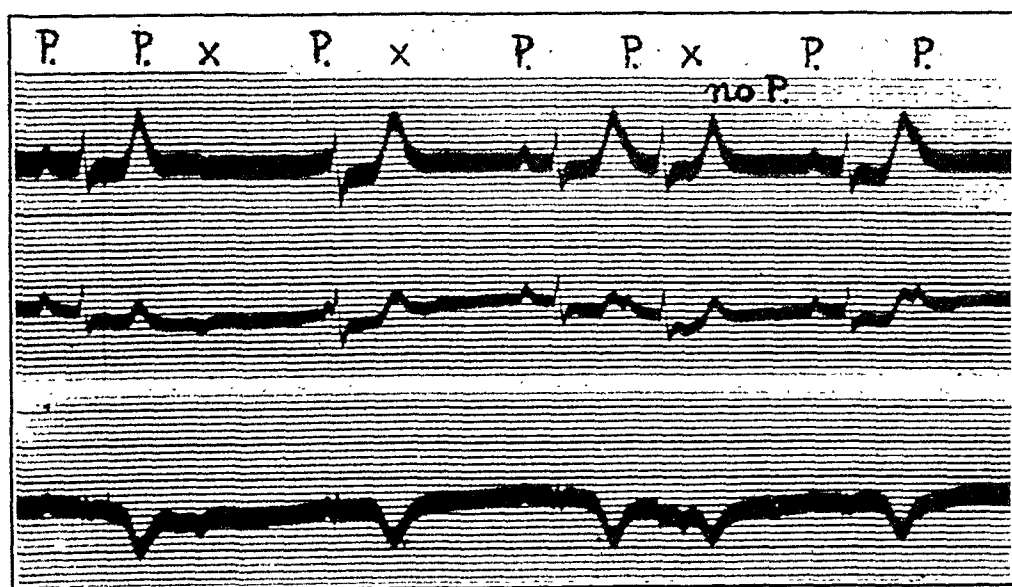


Fig. 13.—Monkey 6 L+R. Taken 65 min. after ligation of right artery. At X auricular extrasystoles (showing in Leads II and III a negative P-wave), not passing to the ventricle, but followed by compensatory pause in P rhythm. Second ventricular complex represents escaped nodal beat. Note 3 to 2 and 2 to 1 A-V block. See also text.

impulses per minute. This 2 to 1 block, however, existed only for about one minute and did not recur. The P-R interval returned to 0.07 sec. and the ventricular rate to about 200. The animal died in about one hour without fibrillation (see above).

*Monkey 6 L + R.*—After ligation of the anterior descending branch an S-T axis developed, as already described, in the mixed field ( $+127^\circ$ ). Before operation the heart rate was 245, the P-R interval 0.07 sec., and the length of ventricular systole 0.15 sec. These did not change after the left ligation (Fig. 12 B). After seven weeks the right coronary artery was ligated. Again there appeared an S-T deviation ( $-160^\circ$ , right field) and a definite secondary coronary electrocardiogram developed with prolongation of the ventricular systole to 0.23 sec. and an interval from the beginning of QRS to the summit of the after-wave of 0.15 sec., being exactly the original length of systole. At first there appeared a 2 to 1 block in which the minimum P-R interval was 0.11 sec., the sinus frequency 202, and the ventricular rate 101. Afterward a remarkable rhythm was discovered (Fig. 12 C and Fig. 13). We noticed sometimes a 2 to 1 and sometimes a 3 to 2 block (dropped beats with Wenckebach's periods), further a temporary 3 to 2 sino-auricular block, and auricular extrasystoles not passing over to the ventricle, but followed by a compensatory pause in the P rhythm. Occasionally there were also escaped nodal beats.



Fig. 14.—Heart of Monkey 6 L + R. Lesion of left ventricular wall and anterior part of septum caused by the first ligation (ramus descendens anterior), which occurred seven weeks previously.

Perhaps in this monkey the auriculoventricular bundle or node became either less conductive or sooner fatigued; it is also possible that the ventricle in lengthening its systole lengthened also its refractory period and thus contributed to the arrhythmia. The blocked auricular extrasystoles point in our opinion to a disturbance of the auriculonodal regions. This animal died some hours after the second ligation, apparently from circulatory failure. There were no indications of fibrillation. The heart clearly showed the result of the left ligation (Fig. 14).

In one case, after ligation of the right coronary artery close to the aorta, the function of the higher pacemaker was obviously practically eliminated, with the consequent gradual development of a slow nodal rhythm.

*Monkey 23 R.*—Within two minutes after ligation of the right artery the S-T deviation was seen, described in Part I, accompanied by after-waves in the opposite direction and prolongation of the ventricular systole from 0.19 to 0.26 sec. After 20 minutes a downward shifting of the pacemaker began;  $P_1$  decreased,  $P_2$  became diphasic, and  $P_2$  negative, all gradually approached R and finally appeared directly in

contact with the ventricular complex (Fig. 15 *D*), so that the negative  $P_{\text{a}}$ , if studied only superficially, might erroneously be taken for a  $Q_{\text{a}}$ -wave. At the same time the heart rate decreased because of the lower frequency of the shifted pacemaker. This heart rate before operation was 171, four minutes after operation 158, twenty minutes after operation 113, and seventy-three minutes after operation 120 per minute.

We have already pointed out in Part I (Cases 23 *A* and 23 *B*) that, while the S-T deviations in Leads I and III (which were in opposite directions) increased, the S-T segment in Lead II tended to become isoelectric (Fig. 15 *B* and *D*). This meant a rotation of the S-T axis of only  $10^\circ$ . Lead II, considered by itself, if no notice be taken of the nodal rhythm, showed a "normal" electrocardiogram, which is once more a warning never to be satisfied with the results of a single lead. Since the after-waves in Leads I and III practically neutralize one another, the prolongation of systole does not become manifest in Lead II, as was also described in Part I. In

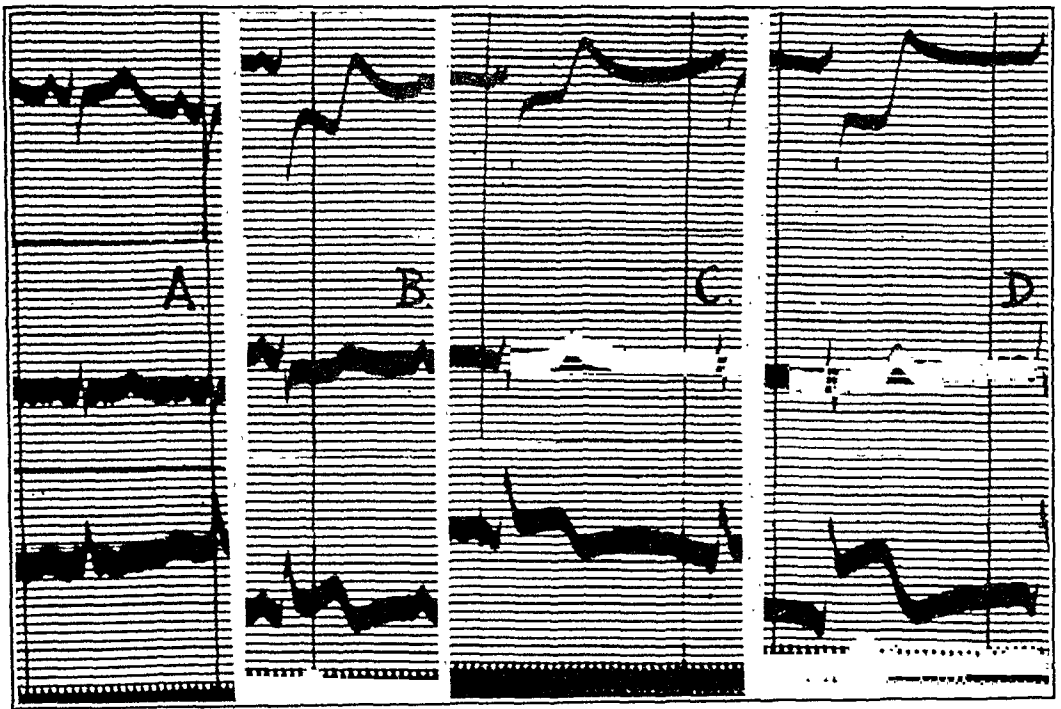


Fig. 15.—Monkey 23 R. *A*, before operation; *B*, 3 min., *C*, 20 min., *D*, 73 min. after ligation of right artery. Nodal rhythm develops. Little change in the ventricular complex of Lead II.

connection with the well-known rule that  $II = I + III$ , the segment *D* of Fig. 15 happens to illustrate the possibility, so often described, of a normal electrocardiogram being built up of two practically monophasic components. This animal died about five hours after the last record was made; there was no evidence of fibrillation, the presumable cause of death being cardiac failure or a gradual fading of the heart automaticity.

Resuming, we may state that after left ligation bundle-branch block was observed, and after right ligation sino-auricular block, auriculo-ventricular block, and shifting of the pacemaker.

A study of these conduction disturbances tends thus to give rise to the impression that in *Macaca* the right coronary artery is of greater significance for the higher centers and conduction paths, including the auriculoventricular node, which in man also is supplied principally by

the right artery;<sup>24</sup> while the left artery in this monkey nourishes the lower strands, namely, the bundle branches.

It appears, however, that often the nonligated vessels can function in a compensating way since many ligations were not followed by conduction disturbances, and such disturbances, even if they developed, sometimes disappeared later.

#### SUMMARY

The arrhythmias and conduction disturbances, observed in several monkeys (*Macaca irus*) after coronary ligation, are described. Extrasystoles were recorded in six out of seventeen monkeys after ligation of the anterior descending branch of the left artery and in six out of fifteen monkeys after ligation of the right artery. The points of origin of the extrasystoles were determined from the electrocardiogram, especially from simultaneous records. The probable cause of these extrasystoles is discussed. Such extrasystoles may, especially if they originate in the apical part of the ventricles and show a tendency to persist for a longer time, bear a localizing character. In two of the monkeys with ligation of the right vessel, ventricular extrasystoles developed into paroxysms of ventricular tachycardia. In one of those a paroxysm could be temporarily checked by a bilateral pressure on the region of the carotid sinus. The possible relation between extrasystoles and fibrillation is discussed. Ventricular fibrillation could be caused experimentally in the monkey by an electrical stimulus at the end of systole. A correlation between extrasystoles and ventricular fibrillation could, however, not be proved with certainty from the observations after coronary ligation. Certainly at least eight of the seventeen monkeys with ligation of the left vessel and two of the fifteen monkeys with ligation of the right vessel died of ventricular fibrillation. The chance of fibrillation after ligation is greatest during the first forty minutes. If it has not developed within about five days, it will probably never set in. Not every death after coronary ligation is due to ventricular fibrillation. Fibrillation after ligation could not be stopped by chemical or physical methods. Bundle-branch block was observed after left ligation; sino-auricular block, auriculoventricular block, and shifting of the pacemaker after right ligation. The relative value of the right and left coronary artery in supplying the different parts of the conduction system in *Macaca* is discussed.

#### REFERENCES

1. de Waart, A., Storm, C. J., and Koumans, A. K. J.: Ligation of the Coronary Arteries in Javanese Monkeys: I. Introduction, General Results, Especially the Changes in the Ventricular Electrocardiogram, *AM. HEART J.* 11: 676, 1936.
2. Kountz, W. B., Prinzmetal, M., and Smith, J. R.: The Effect of the Position of the Heart on the Electrocardiogram (III. Monkey), *AM. HEART J.* 10: 623, 1935.
3. de Waart, A., and Storm, C. J.: Electrocardiographic Observations on Javanese Monkeys, *Act. brev. neerl.* 4: 130, 1934, and *Arch. neerl. de Physiol.* 20: 255, 1935.

4. Lewis, T.: Paroxysmal Tachycardia, *Heart* 1: 43, 1909-10.
5. Maher, C. C., Crittenden, P. J., and Shapiro, P. F.: An Electrocardiographic Study of Viscerocardiac Reflexes During Major Operations, *AM. HEART J.* 9: 664, 1934.
6. Wiggers, C. J.: *Circulation in Health and Disease*, New York and Philadelphia, 1923, p. 431.
7. Owen, S. E.: A Study of Viscerocardiac Reflexes, *AM. HEART J.* 8: 496, 1933.
8. Lewis, T.: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* 1: 98, 1909-10.
9. Condorelli, L.: *Die Ernährung des Herzens und die Folgen ihrer Störung*, Dresden, 1932, Theodor Steinkopff.
10. Damir, A., and Lampert, F.: Veränderungen des Elektrokardiogramms nach Unterbindungen verschiedener Coronararterien zweige, *Ztschr. f. d. ges. exper. Med.* 80: 753, 1932.
11. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
12. Otto, H. L.: The Extracardial Nerves: IV. An Experimental Study of Coronary Obstruction, *AM. HEART J.* 4: 64, 1929.
13. Goldenberg, M., and Rothberger, C. J.: Zur Kenntnis der Extrasystolen nach Unterbindung von Coronargefäßen, *Ztschr. f. d. ges. exper. Med.* 83: 473, 1932.
14. Hinrichs, A.: Beitrag zur Topographie des Herzinfarktes bei akutem Koronarverschluss, *Deutsche med. Wchnschr.* 60: 598, 1934.
15. Hering, H. E.: *Die Karotissinusreflexe auf Herz und Gefäße*, Dresden, 1927, Theodor Steinkopff.
16. de Boer, S.: Paroxysmale Tachykardie, *Ztschr. f. d. ges. exper. Med.* 26: 112, 1922.
17. de Boer, S.: Eine neue Theorie über das Entstehen von Kammerwühlen, *Arch. f. d. ges. Physiol.* 178: 1, 1920.
18. Lewis, T., Drury, A. N., and Iliescu, C. C.: Further Observations Upon the State of Rapid Reexcitation of the Auricles, *Heart* 8: 314, 1921.
19. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia. I. *AM. HEART J.* 6: 522, 1931.
20. Hering, H. E.: Ueber die Koeffizienten, die im Verein mit Koronararterienverschluss Herzkammerflimmern bewirken, *Arch. f. d. ges. Physiol.* 163: 1, 1916.
21. Sands, J., and de Graff, A. C.: The Effects of Progressive Anoxemia on the Heart and Circulation, *Am. J. Physiol.* 74: 416, 1925.
22. Wiggers, C. J.: Studies of Ventricular Fibrillation Caused by Electric Shock. II. *AM. HEART J.* 5: 351, 1930.
23. Hooker, D. R., Kouwenhoven, W. B., and Langworthy, O. R.: Effect of Alternating Electrical Currents on Heart, *Am. J. Physiol.* 103: 444, 1933.
24. Ball, D.: The Occurrence of Heart-Block in Coronary Artery Thrombosis, *AM. HEART J.* 8: 327, 1933.



# THE APPEARANCE OF THE T-WAVE IN LEAD IV IN NORMAL CHILDREN AND IN CHILDREN WITH RHEUMATIC HEART DISEASE

WITH SOME OBSERVATIONS CONCERNING THE CAUSE OF THE T-WAVES OBTAINED\*

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THE value of Lead IV in conditions other than coronary disease has received little attention. The preliminary report by Levy and Bruenn,<sup>1</sup> therefore, stimulated us to investigate more systematically the appearance of Lead IV in rheumatic heart disease. We felt that since many of the patients with this disease were children, it might be advisable to determine the appearance of Lead IV in normal children of various ages and to establish criteria for comparison with children having rheumatic heart disease. We found, for example, that an upright T-wave in Lead IV occurred in many normal children, a finding which has been reported independently by Master and his associates<sup>2</sup> and by Rosenblum and Sampson.<sup>3†</sup> This would make the upright T-wave in Lead IV reported by Levy and Bruenn<sup>1</sup> in rheumatic heart disease less significant in children. In the present study an attempt was made also to evaluate the cause for the changed appearance of Lead IV in normal children and those with rheumatic heart disease.

Four-lead electrocardiograms were obtained in 61 normal children and 5 adolescents; in 20 a second record was obtained at a later date to determine the stability of Lead IV. Four-lead electrocardiograms were also obtained in 31 children, 4 adolescents, and 10 young adults suffering from rheumatic heart disease. Records were obtained in 28 of these during the acute stage and in 29 during the inactive stage. In 24 patients serial curves (from two to four) were obtained during the course of the disease.

The technic employed was that previously described by Katz and Kissin<sup>4</sup> and by Bohning and Katz.<sup>5</sup> The electrode was placed in the fourth interspace just to the left of the sternum. In children of five years or younger a smaller sized electrode (1.5 by 5.0 cm.) was used. During the last nine months, we have used the electrode described by Jenks and Graybiel.<sup>6</sup> Controls showed that curves obtained with the three types of electrodes were identical.

The amplitude of the various deflections in Lead IV was measured, using the level of the curve just before the onset of the P-wave as the zero level. In order to evaluate the effect of age on Lead IV, both the normals

\*From the Heart Station, Michael Reese Hospital.

†This was first described by P. Moia in *Rev. argent. de cardiol.* 2: 26, 1935.

and the patients with rheumatic heart disease were divided into five age groups, viz., (1) birth to 5 years, (2) 6 to 10 years, (3) 11 to 15 years, (4) 16 to 20 years (adolescents), and (5) 21 years or over.

### RESULTS

1. *Normal children.*—A summary of the findings in Lead IV, in the normal children and adolescents is assembled in Table I. While the number of adolescents is small, the findings in this group fall intermediately between those of the adult and child groups. The range of findings in these normal children is shown in Fig. 1.

The P-wave in Lead IV from our study appears to have the same contour range as in the adult except that upright P-waves were more common. The amplitude of  $QRS_4$  (from its most negative to its most positive point) was on the average greater than in the adult. This was due to the fact that the average upright phase of  $QRS_4$  was taller in the normal children than in the adults. The  $\frac{Q}{R}$ -ratio (the ratio of amplitude

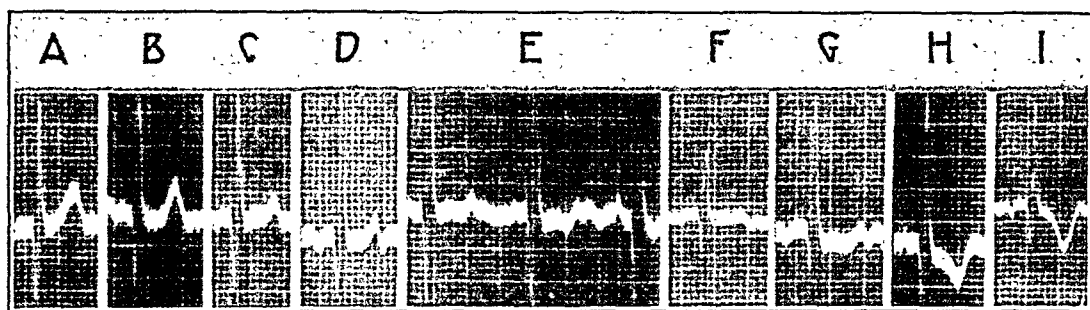


Fig. 1.—Segments of typical Lead IV electrocardiograms obtained from normal children arranged from curves with large upright T-waves on the left to those with inverted ones on the right. The ages of children whose records are shown in segments A to I are  $4\frac{1}{2}$ ,  $1\frac{1}{2}$ ,  $3\frac{1}{2}$ , 8,  $11\frac{1}{2}$ , 13, 10, 15, and 11 years, respectively. Two cycles are shown in segment E to show cyclic variation in contour due to respiration. Discussion in text.

of the negative to that of the upright phase of  $QRS_4$ ) was therefore smaller in children than in the adults. The S- $T_4$  level range in these children was the same as in adults.

The most striking deviation found, which is in accordance with the finding of Moia, Master, and others and of Rosenblum and Sampson, was in  $T_4$ . In contrast with the normal adult groups previously reported by us, in which 49 out of 50 individuals (98 per cent) showed inverted  $T_4$ , in the group of normal children only 26 out of 61 (42 per cent) showed inverted  $T_4$ . In the others,  $T_4$  was either diphasic (with the first phase upright), polyphasic, or upright.  $T_4$  as high as 5 mm. was not infrequent in the children. An inspection of Table II will show that there is a definite correlation with age: the younger the individual, the more likely he is to have an upright T-wave. The oldest child with an upright  $T_4$  was fourteen years of age.

It follows from this that an upright, diphasic, or polyphasic  $T_4$  in young children, contrary to the findings in adults, cannot by itself be

TABLE I

SUMMARY OF APPEARANCE OF LEAD IV IN NORMAL ADULTS, ADOLESCENTS, AND CHILDREN, AND IN CHILDREN WITH RHEUMATIC HEART DISEASE

	NO. OF INDIVIDUALS	P <sub>1</sub> AMP.*		Q <sub>4</sub> AMP. (1ST NEG. DEFLECT. OF QRS <sub>1</sub> )		R <sub>4</sub> AMP. (UPRIGHT DEFLECT. OF QRS <sub>1</sub> )		QRS <sub>4</sub> TOTAL AMP. (FROM PEAK OF Q <sub>4</sub> TO R <sub>4</sub> )		$\frac{Q}{R}$ RATIO (RELATIVE AMP. OF Q <sub>4</sub> TO R <sub>4</sub> )		S-T <sub>1</sub> LEVEL		T <sub>4</sub> AMP.	
		AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE
Normal adults†	50	-0.6	+1.0	-8.5	-1.0	+13.5	+2.0	22.5	5.0	-	-	-1.2	0.0	-4.4	+1.0
			-1.5	-19.0		+33.0		39.0		-		-2.0		-10.0	
Normal adolescents	5	0.0	+1.0	-8.0	-6.0	+18.0	+12.0	26.0	19.0	0.5	0.3	-1.4	-0.5	-5.4	-2.0
			-1.5	-10.0		+21.0		31.0		0.6	0.6	-1.5		-9.0	
Normal children	61	0.0	+2.0	-8.5	-1.0	+17.0	+3.0	26.0	7.0	0.5	0.1	-0.6	0.0	-0.3	+5.0
			-1.5	-19.0		+40.0		57.0		2.0	2.0	-2.0		-6.5	
Inactive stage	17	0.0	+2.0	-11.0	-4.0	+23.0	+8.0	31.0	15.0	0.4	0.1	-0.9	+3.0	-1.1	+6.0
			-2.0	-25.0		+40.0		50.0		1.7	1.7	-2.0		-6.5	
Acute stage	25	0.0	+2.0	-8.0	-1.0	+21.0	+6.0	29.0	12.0	0.4	0.05	-0.8	+2.0	+1.8	+6.0
			-2.0	-24.0		+40.0		50.0		2.0	2.0	-3.5		-4.0	

\*All amplitude measurements are in millimeters.

No. = number

Amp. = amplitude

Deflect. = deflection  
Neg. = negative.†Taken from the data of Katz and Klissin<sup>4</sup> and Bohning and Katz<sup>5</sup>.

TABLE II  
APPEARANCE OF T-WAVE IN LEAD IV IN NORMAL INDIVIDUALS AND PATIENTS WITH ACUTE OR INACTIVE RHEUMATIC  
FEVER CLASSIFIED ACCORDING TO AGE

AGE RANGE		BIRTH TO 5 YR.			6 TO 10 YR.			11 TO 15 YR.			16 TO 20 YR.			21 YR. OR OVER		
Type of case		N	A	I	N	A	I	N	A	I	N	A	I	N	A	I
No. of individuals		14	3	3	17	14	6	30	8	8	5	1	4	50*	2	8
Amp.† of T <sub>1</sub>	{ Av.	+0.9	+2.0	+2.0	+0.6	+1.7	-1.0	-1.1	+1.8	-2.1	-5.4	+2.5	-0.3	-4.4	-1.0	-2.2
	{ Range	+5.0	+6.0	+6.0	+5.0	+5.0	+6.0	+4.0	+6.0	0.0	-2.0	+2.5	+3.0	+1.0	0.0	+1.5
% with upright, di-		-4.0	-2.0	-5.0	-3.0	-4.0	-6.5	-6.5	-2.0	-5.0	0	+2.5	-2.0	-10.0	-2.0	-6.0
% with inverted T <sub>1</sub>		71	67	67	58	93	50	50	75	25	100	0	75	2	50	50

\*Taken from the data of Katz and Kissin<sup>4</sup> and Bohning and Katz<sup>5</sup>  
Amp. = amplitude  
Av. = average  
% = per cent

N, normal subjects  
A, patients with acute stage of rheumatic fever  
I, patients with inactive stage of rheumatic fever.  
†All amplitude measurements are in millimeters.

taken as evidence of heart disease. Changes in  $QRS_4$  and  $S-T_4$  recognized as indicating abnormality in adults have the same significance in childhood. An upright  $P_4$  in childhood is not uncommon.

2. *Rheumatic Heart Disease in Childhood—Value of Single Records.*—With our analysis of normal children as a base we tried to interpret the findings in children with rheumatic heart disease. The results of the measurements are summarized in Table I. In cases in which more than one curve was obtained in the active stage, the curve used was the one taken when the patient showed the greatest degree of activity. In this analysis abnormalities in rhythm and in A-V and intraventricular conduction were ignored, attention being paid only to the contour and amplitude of the various deflections in Lead IV.

No significant deviation in  $P_4$  was noted in this series as compared with the normal controls. However, large  $P_4$  waves of long duration outside the normal range were found in patients with long-standing mitral stenosis; this was associated with large, broad, upright or diphasic P-waves in the standard three leads. No significant changes in the  $QRS_4$  group were seen in this series except for disturbances in intraventricular conduction, viz., prolongation of  $QRS_4$  span, slurring and notching, and M- and W-shaped complexes. However,  $QRS_4$  complexes mainly up with only small  $Q_4$ -waves (first negative phase of  $QRS_4$ ) were frequently encountered.  $S-T_4$  deviations outside the normal range occurred twice in patients with long-standing rheumatic heart disease; both were elevated above the isoelectric level. In four patients deviations of the  $S-T_4$  segment appeared only in the acute stage; in three of these  $S-T_4$  was elevated; in one it was depressed 3.5 mm. (which is outside the normal limit of 2 mm.).

While the appearance of T in Lead IV was not strikingly different in individual children with rheumatic fever from those in the normal control group, upright, diphasic, and polyphasic  $T_4$ -waves were more frequent in rheumatic heart disease, especially in the active stage. This was true in all age groups as shown in Table II. The T-wave in Lead IV showed no peculiarities in rheumatic fever not seen in the normal control children.

From this analysis it would seem that in a single record a tall and broad  $P_4$ , an absence of the  $Q_4$  (the first negative phase of  $QRS_4$ ), deviations of  $S-T_4$  (more than 2 mm. below or any extent above the isoelectric line), prolonged span, marked notching, and triphasic appearance of  $QRS_4$  are the only signs of disease of the heart to be obtained in childhood from Lead IV. None of these abnormalities is specific for rheumatic fever. In contrast to the adult, the contour of the T-wave in Lead IV in a single record is apparently of no diagnostic value in childhood.

3. *Rheumatic Heart Disease—Serial Records.*—Serial curves were obtained in twenty-four patients. While the series is small, certain deduc-

tions seem justified. As the activity of the rheumatic infection subsided, there was a tendency for the first negative phase of  $QRS_4$  to increase in depth; that is, the  $\frac{Q}{R}$  ratio increased. This did not occur in

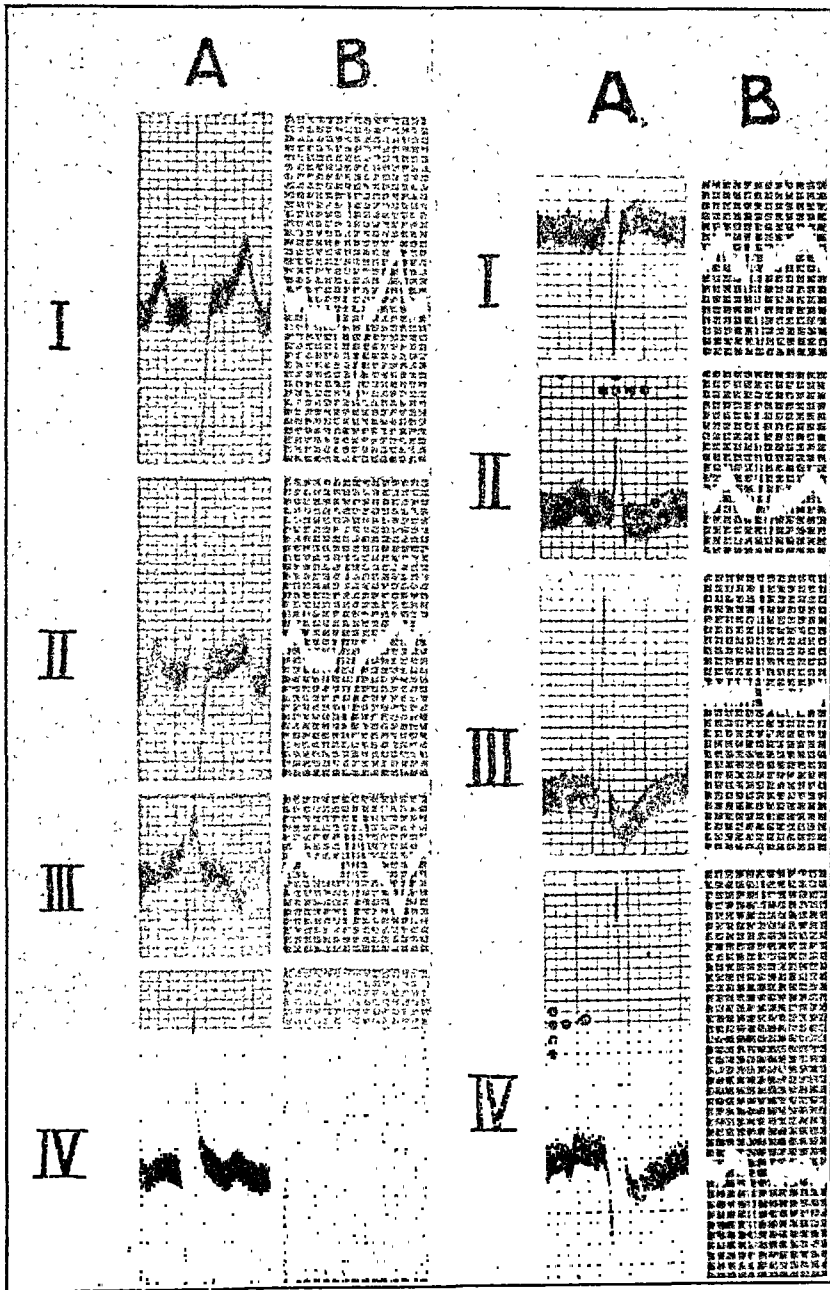


Fig. 2.

Fig. 3.

Fig. 2.—Four-lead electrocardiograms obtained in an eleven-year-old boy with recurrence of acute rheumatic fever and evidence of an old mitral and aortic valvulitis. The acute attack started three weeks before curve A was obtained. Curve B was obtained a week later. The patient's course was downhill, and he died three weeks after curve B was taken. Discussion in text.

Fig. 3.—Four-lead electrocardiograms obtained in a thirteen-year-old girl with active rheumatic fever of several months' duration, who showed congestive heart failure and pericardial effusion at the time curve A was taken. Curve B was taken two months later, patient being slightly improved. Patient was discharged, improved, one month later. Discussion in text.

every instance but sufficiently frequently to merit investigation in a larger series.

$S-T_4$  deviations outside the normal range occurred three times in this series. In one patient (Fig. 2) the  $S-T$  deviated more from the normal

in later records. This was associated with a progressive intraventricular block; the patient had a persistent septic temperature and died three weeks after the last record was taken. In a second patient the S-T<sub>4</sub> deviation appeared three months after the onset of the active rheumatic fever and the patient died three weeks later. In the third patient (Fig. 3) the S-T<sub>4</sub> deviation appeared during the active stage and disappeared in a later record taken after the patient had improved clinically. The S-T<sub>4</sub> deviation was, in this case, associated with S-T deviations in the standard leads. In the last two patients there was clinical evidence of pericardial effusion, and the changes were probably due to pericardial tamponade (Katz, Feil, and Scott<sup>7</sup>).

As regards the T<sub>4</sub>-wave, the patients could be divided into three groups: Group I (thirteen cases) had upright T<sub>4</sub>-waves during the acute stage of the rheumatic fever, and the T-waves became diphasic, polyphasic, or inverted as the patients showed clinical signs of improvement (Figs. 4 and 5). In four of these the variation in contour was confined to Lead IV. This is in accord with the observations reported by Levy and Bruenn.<sup>8</sup> In this group the inversion of the T-wave occurred early while the sedimentation rate was still rapid and the clinical signs of activity were definite.

Group II (five cases) showed no change in T<sub>4</sub> in the serial curves. Of these one had an upright T<sub>4</sub>; one had an inverted T<sub>4</sub>; and three had diphasic T<sub>4</sub>-waves. In these patients the standard leads were also normal and did not show any significant changes in the serial records. Three of these patients had evidence of active rheumatic heart disease in the form of valvular involvement. The other two had chorea with very mild rheumatic heart disease.

Group III (six cases) showed inverted or diphasic T<sub>4</sub>-waves in the active stage, and later the T-wave became upright. In all of these the standard leads were abnormal in some regard, and the contour in the successive records changed. Four of these patients showed progressive involvement of the heart and persistent activity; two of these died. Two other patients in this group, however, showed signs of decreased activity and clinical improvement (Fig. 6).

Thus, while there is a fair degree of parallelism between the changes in the T<sub>4</sub> and the clinical course, certain discrepancies were present in several instances in Groups II and III.

4. *Normal Children—Serial Records.*—It was because of this discrepancy that we determined to investigate the constancy of Lead IV in normal children. In adults we (Bohning and Katz<sup>5</sup>) found that the contour of Lead IV is constant within narrow limits. In 20 children Lead IV was repeated from six to eight months after the first record; in 10 of these the second record showed no significant deviation from the first (S<sub>1</sub>, Fig. 7); in 7 the second record showed a more negative T<sub>4</sub> or a change from an upright to an inverted T<sub>4</sub> (S<sub>2</sub>, Fig. 7); in the

other 3 the second record showed a more upright  $T_4$  or a change from an inverted to an upright  $T_4$  ( $S_3$ , Fig. 7). In some instances, as in  $S_2$  (Fig. 7), no change in  $QRS_4$  appeared; in others, as in  $S_3$  (Fig. 7),  $QRS_4$  was altered.

Apparently then the T-wave in Lead IV is not as stable in normal children as in normal adults; nor is T as stable in Lead IV as in the

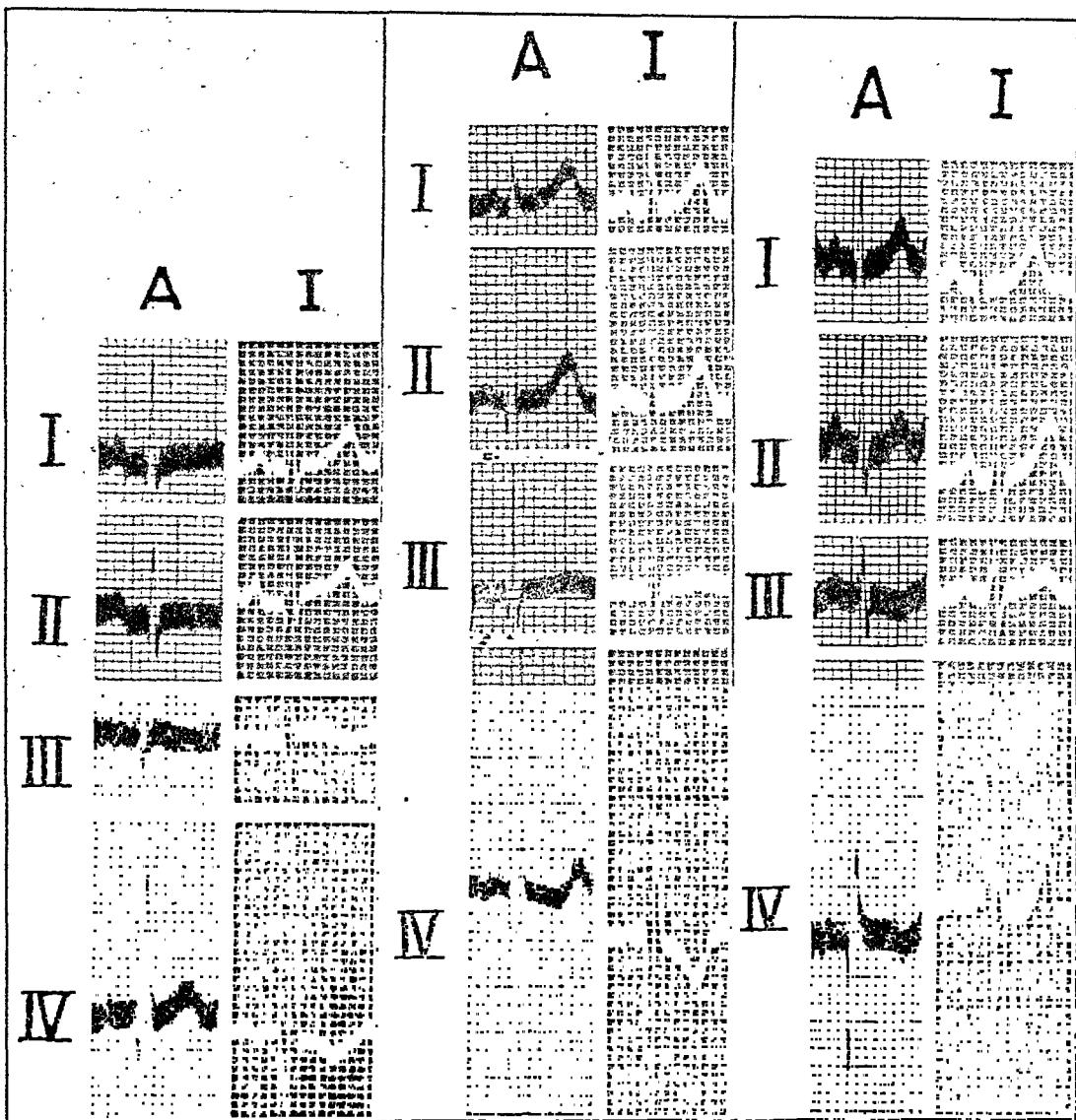


Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Four-lead electrocardiograms obtained in a nine-year-old boy with a first attack of acute rheumatic fever. Curve A taken ten days after onset of symptoms. Curve I taken two and one-half months later with patient apparently recovered. Discussion in text.

Fig. 5.—Four-lead electrocardiograms obtained in a four-and-one-half-year-old boy with a first attack of acute rheumatic fever. Curve A taken four weeks after onset of symptoms. Curve I taken one month later with patient apparently recovered. Discussion in text.

Fig. 6.—Four-lead electrocardiograms obtained in a two-and-one-half-year-old boy with a first attack of acute rheumatic fever. Curve A obtained during acute stage. Curve I taken two months later with patient apparently recovered. Discussion in text.

standard three leads of the child. This must be considered in interpreting the effects of acute rheumatic fever and rheumatic heart disease on serial electrocardiograms in children. It helps to explain some of



the discrepancies between the clinical course and the  $T_4$  changes noted above. It would seem, therefore, that even serial electrocardiograms in children with rheumatic heart disease must be cautiously interpreted as evidence of progression or recovery.

#### DISCUSSION OF FINDINGS, WITH SOME FURTHER OBSERVATIONS AND THEORETICAL CONSIDERATIONS

The explanation for the presence of upright T-waves in Lead IV in normal children must be sought in differences (1) in the position of the heart in the chest due to (a) shift in its anatomical long axis, (b) rota-

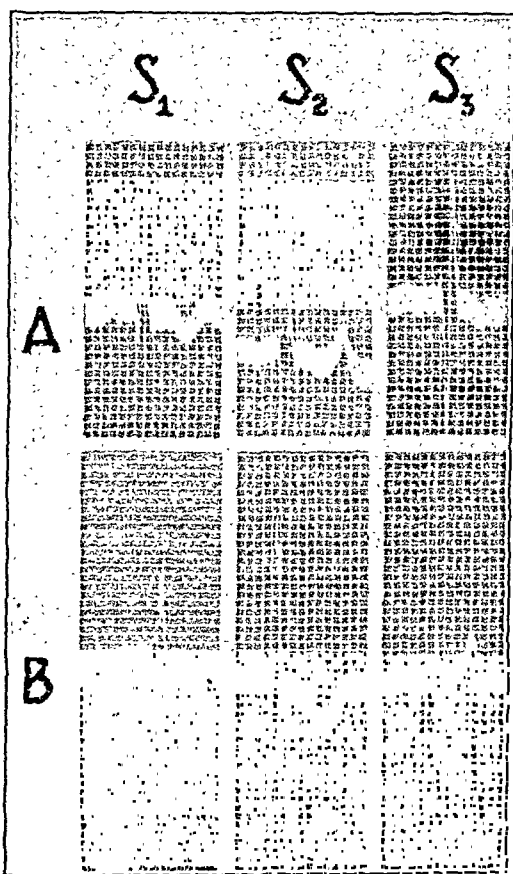


Fig. 7.—Lead IV records obtained in three normal children to show the variability found in some of these normal children when serial curves are taken:  $S_1$ , a girl aged eight years;  $S_2$ , a boy aged ten years; and  $S_3$ , a boy aged five years. Curves A were obtained in February, 1935, curves B, in October, 1935. Discussion in text.

tion of the heart on its transverse or sagittal axes, or (c) the relative size and shape of the ventricles; (2) in the contact of the heart with the chest wall, the extent and position of the precordial area not covered by lung, the thinness of the chest wall, or the shape and size of the chest cavity. (Upright  $T_4$ -waves tended to be more frequent in children with thin chest walls and narrow thoracic cages.) These various factors can alter the electrocardiogram in Lead IV since the precordial electrode is placed in relation to a bony landmark of the chest and does not bear the same relation to the heart in children that it does in adults.

It is well known that the heart in children differs from the heart in adults in the sense that (a) the ratio of right ventricular weight to left ventricular weight is increased, especially in early childhood, and moderate right axis shift of the electrocardiogram is more common, (b) the heart tends to lie more horizontally, (c) the right ventricle forms more of the left half of precordial dullness and (d) may lie more intimately in contact with the anterior chest wall (Lincoln and Spillman,<sup>9</sup> Bakwin and Bakwin,<sup>10</sup> and Roesler<sup>11</sup>). There is some evidence that these factors might cause the upright T. Thus, White<sup>12</sup> reported that T<sub>4</sub> was usually upright in cor pulmonale and the tetralogy of Fallot. In a series of seven adult patients which we have assembled with right axis shift due to varying types of heart disease such as cor pulmonale, mitral stenosis, congenital heart disease, or displacement of the heart to the right, T<sub>4</sub> was upright only on occasion (Table III). On the other hand, in a series of sixteen adults patients with left axis shift due to hypertension, rheumatic and syphilitic aortic insufficiency, and congenital heart disease, T<sub>4</sub> was inverted in all instances, provided patients with coronary sclerosis were excluded (Table III). In twenty of the normal children a direct correlation was made between T<sub>4</sub> and the axis deviation in the standard leads. Five of these twenty normal children showed right axis deviation, and fifteen did not; 80 per cent of the children with right axis deviation had T<sub>4</sub> upright while only 30 per cent of those without right axis deviation had T<sub>4</sub> upright (Rosenblum and Sampson,<sup>3</sup> however, could obtain no such correlation in fifty children). This correlation together with the observations in adults with right and left ventricular preponderance indicates that axis deviation to the right is an important factor—but not the only one—responsible for the appearance of an upright T<sub>4</sub> in normal children.

Evidence in line with this is the fact that we have found that in the majority of normal adults, upright or diphasic T-waves are obtained when the precordial lead is placed in the fourth interspace to the right instead of the left of the sternum (Table III). This is also the case usually in adults with right axis deviation, but in those with marked left axis deviation the T-wave with this precordial lead is negative (Table III).

These observations and others which we will report in future communications led us to investigate the electrical field during the inscription of the T-wave.

As a start, we took records with the distant electrode on the left leg and the precordial electrode in four different regions of the anterior chest located somewhat like those used by Kossmann and Johnston,<sup>13</sup> all in the fourth intercostal space, to wit: (a) just to the right of the sternum, (b) just to the left of the sternum (the standard Lead IV we employ), (c) in the left midclavicular line, and (d) in the left anterior axillary line. Such records we have now obtained in over 100 patients.

TABLE III  
APPEARANCE OF T IN VARIOUS PRECORDIAL LEADS USING THE LEFT LEG  
FOR THE SECOND ELECTRODE

ADULT OR CHILD	PRECORDIAL LEAD IN 4TH INTERSPACE			
	TO RIGHT OF STERNUM	TO LEFT OF STERNUM	IN MID- CLAVICULAR LINE	IN ANTERIOR AXILLARY LINE
<i>Normals</i>				
A	+2	-9	-7	- $\frac{1}{2}$
A	-2	-8	-7	-2
A	+2	-5 $\frac{1}{2}$	-6 $\frac{1}{2}$	-1 $\frac{1}{2}$
A	-1, +2	-9	-13	-3 $\frac{1}{2}$
A	+2 $\frac{1}{2}$	-8	-7	-4
A	+2	-6	-5	0
A	-2, +1 $\frac{1}{2}$	-5	-3.5	-1
A	-1, + $\frac{1}{2}$	-4 $\frac{1}{2}$	-3	-1.5
A	-1, +3	-12	-7	-1.5
A	-1, +2 $\frac{1}{2}$	-5 $\frac{1}{2}$	-4	-2
C ( 9 yr.)	+3 $\frac{1}{2}$	-4	-6	-4
C (10 yr.)	+3	+1, -1	-3	-3 $\frac{1}{2}$
C (10 yr.)	+5	-2 $\frac{1}{2}$	-4 $\frac{1}{2}$	?
C ( 6 yr.)	+4	-2	-4	-3
C (11 yr.)	+2	-6	-6 $\frac{1}{2}$	-3
C ( 7 yr.)	+5	+4	-5	-2
C ( 9 yr.)	+6	+2	-2	-5
<i>Right Ventricular Preponderance</i>				
A	+2	-2	-9	+1
A	+ $\frac{1}{2}$	+ $\frac{1}{2}$ , - $\frac{1}{2}$	-1 $\frac{1}{2}$	-2
A	-1 $\frac{1}{2}$	-1	+2	- $\frac{1}{2}$
A	+6	+5	+7	+1
A	-4	-4	?	+5
A	+2	+3	-7	+3
A	+1	-8	-5	-3
C ( 5 yr.)	+8	+12	+3, -1	-5
C (15 yr.)	+4 $\frac{1}{2}$	+3	-2	-1
C ( 9 yr.)	+6	-6	-7	-5
C (10 yr.)	+8	-6	-12	-5 $\frac{1}{2}$
C (12 yr.)	+3	+1	-1	-6 $\frac{1}{2}$
C (13 yr.)	+2	+1 $\frac{1}{2}$	-1	-1
C ( 8 yr.)	+3	+2	-3	-4
<i>Left Ventricular Preponderance</i>				
A	-2	-5	-7	-1
A	-2	-3	-1 $\frac{1}{2}$	+4 $\frac{1}{2}$
A	-1 $\frac{1}{2}$	-4 $\frac{1}{2}$	-1 $\frac{1}{2}$	+1 $\frac{1}{2}$
A	-1	-3	+1	+1
A	-3	-3	+ $\frac{1}{2}$	+1
A	-2 $\frac{1}{2}$	-3	-1	+1 $\frac{1}{2}$
A	-1	-2	+ $\frac{1}{2}$	+2 $\frac{1}{2}$
A	-1 $\frac{1}{2}$	-3	+6	+4 $\frac{1}{2}$
A	-10	-7	+13	+5
A	-4	-4	-1	+1 $\frac{1}{2}$
A	-4	-3	+4	+2
A	-6	-13	+4	+10
A	-9	-15	-2	+4 $\frac{1}{2}$
A	-5	-10	-5	+2
A	-3	-6	-2	+6
A	-3	-10	-3	+4 $\frac{1}{2}$

For this study we have confined ourselves to an analysis of the height of the T-wave in normal adults and children and those showing right and left ventricular preponderance. The results are assembled in Table III, and the significant findings have already been referred to. It was obvious, after these data were assembled that too few points had been explored to give an adequate idea of the electrical field during the inscription of T. In eleven individuals, therefore, a larger number of points were explored over the chest anteriorly and posteriorly. The subjects were kept in the reclining position while the precordial electrode was shifted, the other electrode being fixed on the left leg. A similar method has been used by Groedel and Koch<sup>14</sup> recently for the QRS complex. Both of these methods are an application of Waller's concept of the electrical field. The electrocardiograms so obtained give the relative potential of the exploring electrode with respect to the leg and not the absolute potential. However, the leg electrode is placed so far from the heart that its potential changes during the inscription of T are not great. An inspection of some of the records reported by Wilson and his associates<sup>15</sup> purporting to give the absolute potential\* of the leg shows the magnitude to be within 0.1 millivolt. In determining the potential, the height and direction of the T-wave were used. It is appreciated that the time of inscription of this point is not synchronous in the different precordial leads employed. But this error is also of little significance for the use we intend in this report. While our method, for the reasons given, is to be considered only a first approximation, it nevertheless revealed definite information. More precise exploration of the electrical field for all phases of the heart cycle is in progress in this laboratory and will be reported at another time.

The data obtained in several subjects are shown diagrammatically in Figs. 8 to 14. In Fig. 8 is shown the potential of various regions in a twenty-three-year-old adult with normal standard leads and with a Lead IV well within the mean of normal limits. The line defining the potential equal to that in the leg is clearly shown. It is interesting that the line of "leg potential" runs cephalad in the midsternal line to the level of the third rib and then runs obliquely upward over toward the left arm, reaching its crest at the level of the second rib and then running obliquely downward toward the back. In the back it descends somewhere along a line over the left scapular angle. In this subject the relatively negative potential (the height of the upright T-waves) was nowhere as great as the relatively positive potential (the depth of the negative T-waves), but the area in the chest occupied by the former was much greater. Furthermore, the lines of equipotential (equal T-wave amplitudes) are much closer over the sternum and precordium than elsewhere.

In Fig. 9 is shown a similar analysis of a child aged nine and one-half years who had a negative T<sub>4</sub>; the electrical field during the peak

\*This idea of Wilson's has recently been seriously questioned by Storti.<sup>16</sup>

Fig. 8.

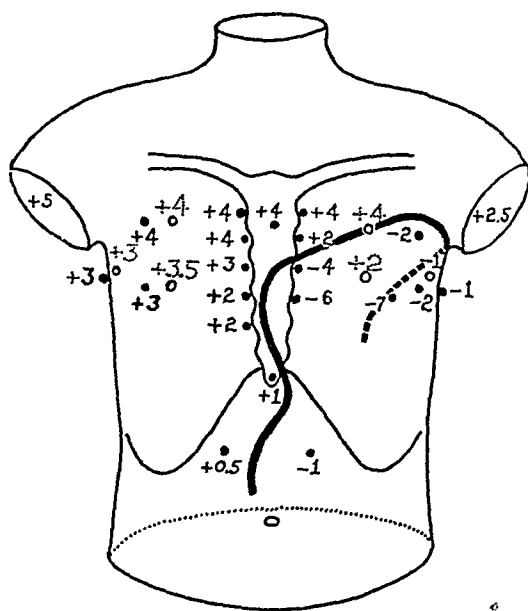


Fig. 9.

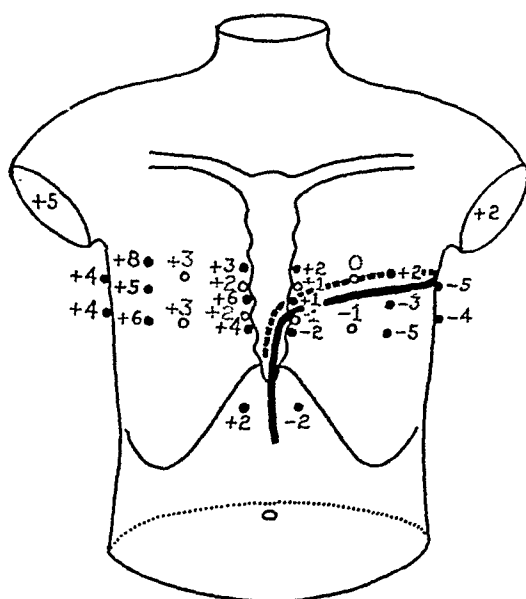
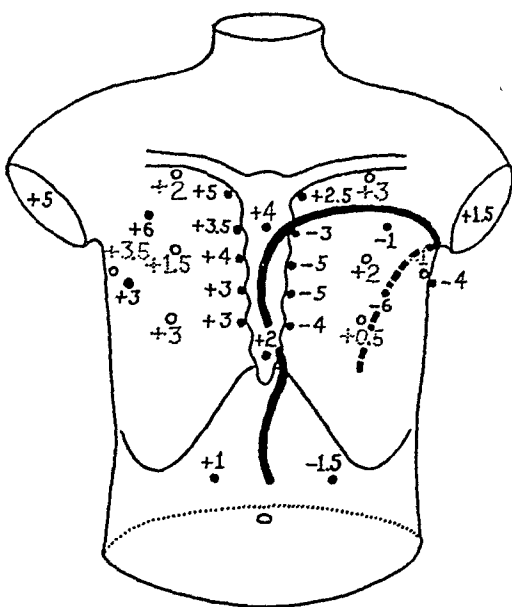


Fig. 10.

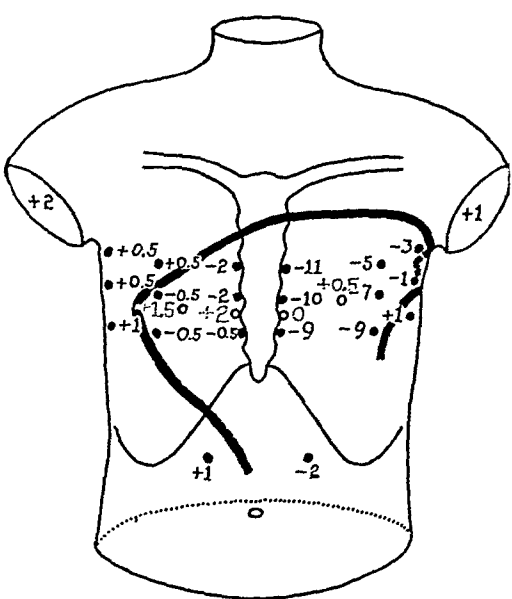


Fig. 11.

Fig. 8.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of leg in a normal twenty-three-year-old man with a normal four-lead electrocardiogram. (+ indicates an upright and -, an inverted T-wave). Solid circles and solid figures are on anterior surface or anterior half of lateral surface of chest, open circles and dotted figures, on posterior surface or on posterior half of lateral surface of chest. Heavy line marks the course of potential during peak of T equivalent to that in leg, the so-called "leg potential" line. It is marked out as a solid line when on anterior surface or anterior half of lateral surface and is marked out as a dotted line when on posterior surface or posterior half of lateral surface of chest. Discussion in text.

Fig. 9.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a normal nine-and-one-half-year-old child with  $T_1$  inverted. Conventions as in Fig. 8. Discussion in text.

Fig. 10.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a normal nine-year-old child with  $T_1$  upright. Conventions as in Fig. 8. Discussion in text.

Fig. 11.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a fifty-six-year-old man with marked left ventricular preponderance. Conventions as in Fig. 8. Discussion in text.

Fig. 12.

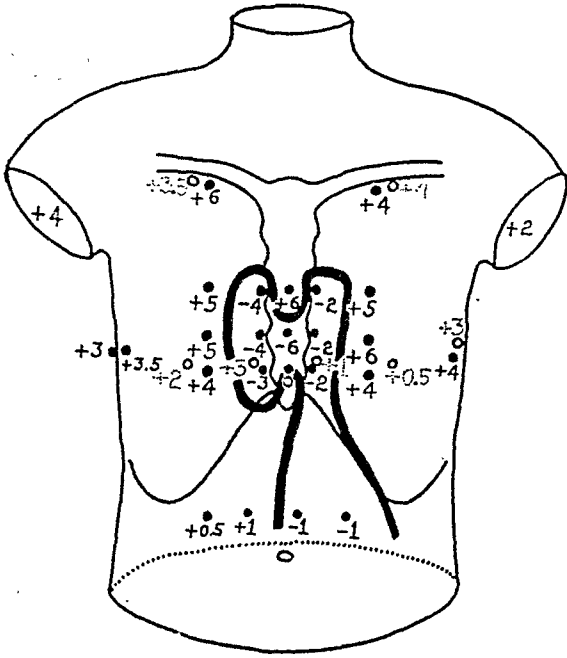


Fig. 13.

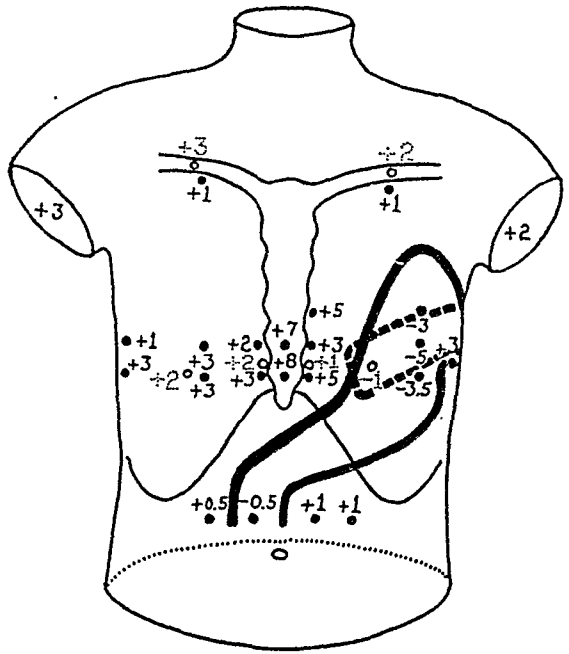


Fig. 14.

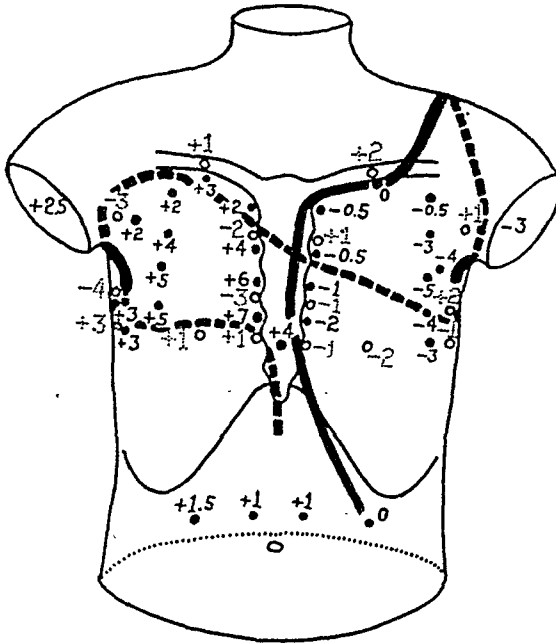


Fig. 12.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a forty-eight-year-old man with right ventricular preponderance. Conventions as in Fig. 8. Discussion in text.

Fig. 13.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a forty-six-year-old woman with right ventricular preponderance. Conventions as in Fig. 8. Discussion in text.

Fig. 14.—Diagram showing the magnitude of the T-wave in various spots on the chest (and in the two arms) as compared with that of a leg in a fifty-year-old man with congenital heart disease, having QRS inverted in all three of the standard leads. Conventions as in Fig. 8. Discussion in text.

of T and the line of "leg potential" was practically, though not absolutely, the same as in the preceding adult. In Fig. 10 is shown a similar analysis of one child aged nine years who had a positive  $T_4$ . It will be seen that more of the chest points have upright T-waves than are shown in the preceding two charts and that the line of "leg potential" does not rise as high on the chest as in the preceding subjects. In a second child aged seven years who had a positive  $T_4$ , the line of "leg potential" had shifted to the left anterior axillary line and went as high as the second interspace. Unfortunately the posterior part of the chest in this child had not been explored, but the T-wave was upright over the entire chest anteriorly.

In both patients with left ventricular preponderance, the T-wave was negative over the anterior chest wall and positive over the lateral and posterior walls. The line of "leg potential" was near both lateral walls of the chest and crossed high up on the chest anteriorly (Fig. 11). In right ventricular preponderance, of which we have analyzed two cases with, and two without congenital heart defects, the area over which negative T-waves are obtained was markedly reduced (Figs. 12 and 13), but in each the line of "leg potential" took a different course.

The changes described in these conditions might all be conceived as simply being due to a complex rotation of the resultant vector set up in the heart. That this simple concept cannot suffice is shown by the fact that exploration of the field in a fifty-year-old subject with congenital heart disease having inverted QRS complexes in the standard three leads showed a very complex arrangement of the line of "leg potential" (Fig. 14). In viewing the chest at most horizontal levels, four lines of "leg potential" are seen separating areas having positive, from those having negative, T-waves. This observation, however, would fit with the concept promulgated in this laboratory (Katz and Korey<sup>17</sup>) that the electrical field is determined in large part by the nature of the electrical conductors in contact with the heart. According to the study upon which this concept was based, the lungs are poor electrical conductors while the posterior paravertebral muscle mass, the diaphragm, and the anterior chest wall where lung is absent are the good conductors. Thus in this patient with congenital heart disease it would seem that the currents set up from the posterior good conductors and those set up from the diaphragm and anterior chest wall interfere with each other so that the result might be regarded as similar to the action of two bipoles not in line. Investigations are in progress to see whether this holds also in other conditions. At present we can say that there is no evidence opposed to the idea that the electrical field in all cases is the resultant of currents spreading in the body from various regions of the heart in contact with good conductors. When the position of the heart is altered in relation to these good and poor electrical conductors

and when the position in these good and poor electrical conductors in the chest is altered, the whole electrical field is changed. The effect would be more marked over the chest since the lines of equipotential are closer together than in the extremities.

The division of children into those having a negative T-wave and those with a positive T-wave in Lead IV fits the clinical and x-ray observations that children can be divided into those with "puerile" and those with "adult" chests, and that the adult type of chest occurs as early as four years.<sup>15</sup> It is thus possible in children to have the line of "leg potential" run anteriorly anywhere from the middle of the sternum to the left anterior axillary line and have the crest at any level. The variations of  $T_1$  in different normal children can be explained on the variable degree of transition from the "puerile" to the "adult" chest type.

The variability of  $T_1$  contour in successive records of the same child is also to be accounted for on the basis that the line of "leg potential" is close to the position of the precordial electrode ordinarily used in Lead IV and that the lines of equipotential are close together in this locality. Consequently the electrical field could be altered sufficiently by changes in the position of the heart such as might result from shifts in the diaphragm because of gas or food in the gastrointestinal tract, or might result from small differences in posture of the body when the several records were taken. Since the heart in the child is more mobile than in the adult, such changes in  $T_1$  are more to be expected in children than in adults. Respiratory changes of  $T_1$  in children are very common and are more marked than in adults.

The contour of  $T_1$  in acute rheumatic heart disease is determined not only by the factors enumerated above for the normal children but also by two other factors. The first is the result of the active infection of the myocardium. In rare instances it may be the result of pericarditis with effusion or still more rarely of coronary endarteritis with resultant local areas of myocardial ischemia. The second is the result of long-standing involvement of the heart, either the result of the myocardial damage or of changes in heart size, shape, and position which cardiac dilatation and the associated mitral and aortic valvular deformities may have led to. The changes due to the active process tend to disappear when the activity of the infection subsides and are progressive if the acute process advances. The changes due to the chronic damage persist after the active stage has disappeared and change but slowly.

The only clinical problem in rheumatic heart disease as far as Lead IV is concerned is to differentiate changes due to the rheumatic process from those which are normal in childhood and to determine whether changes in successive records are evidence of changes in the rheumatic process and its effects or are normal variations to be encountered in children.



## SUMMARY AND CONCLUSIONS

1. Upright diphasic or polyphasic T-waves in Lead IV are common in normal children, especially in the younger age groups.

2. The contour of Lead IV in normal children may alter considerably when curves are repeated a few months apart.

3. Children with active rheumatic heart disease show a higher percentage of upright T-waves in Lead IV than do normal children of the same age. The T-wave tends to become inverted when recovery from the acute stage sets in and tends to become more upright when the disease process becomes aggravated. However, exceptions to these correlations are not uncommon.

4. An analysis was made of the factors which may be responsible for the differences in the T-wave of Lead IV between children and adults, as well as between normal children and children with rheumatic heart disease.

5. The electrical field at the surface of the body during the inscription of the T-wave was examined in a variety of conditions, with the result that a new view concerning the causes and significance of the upright and inverted T-waves in precordial leads was revealed.

6. As a result of the present study, it is concluded that the practical value of Lead IV in children suffering from rheumatic heart disease is definitely limited. Single records in individual cases add no valuable information, and serial curves supply data which may be suggestive and are only confirmatory to that obtained from the ordinary standard three leads.

We are indebted to the medical staff of the Sarah Morris Hospital for Children and of the Children's Cardiac and Pediatric Clinics in Mandel Clinic for their courtesy in permitting us to study their patients. The assistance of Dr. H. Wachtel is acknowledged.

## REFERENCES

1. Levy, R. L., and Bruenn, H. G.: *Proc. Soc. Exper. Biol. & Med.* 32: 559, 1934.
2. Master, A. M., Dack, S., and Jaffee, H. L.: *Proc. Soc. Exper. Biol. & Med.* 32: 1529, 1935.
3. Rosenblum, H., and Sampson, J. J.: *AM. HEART J.* 11: 49, 1936.
4. Katz, L. N., and Kissin, M.: *AM. HEART J.* 8: 595, 1933.
5. Bohning, A., and Katz, L. N.: *Am. J. M. Sc.* 189: 833, 1935.
6. Jenks, J. L., and Graybiel, A.: *AM. HEART J.* 10: 693, 1935.
7. Katz, L. N., Feil, H. S., and Scott, R. W.: *AM. HEART J.* 5: 77, 1929.
8. Levy, R. L., and Bruenn, H. G.: *AM. HEART J.* 10: 881, 1935.
9. Lincoln, E. M., and Spillman, R.: *Am. J. Dis. Child.* 35: 791, 1928.
10. Bakwin, H., and Bakwin, R. M.: *Am. J. Dis. Child.* 49: 861, 1935.
11. Roesler, H.: *Am. J. Roentgenol.* 32: 464, 1934.
12. White, P. D.: *Ann. Int. Med.* 9: 115, 1935.
13. Kossmann, C. E., and Johnston, F. D.: *AM. HEART J.* 10: 925, 1935.
14. Groedel, F. M., and Koch, Eb.: *Ztschr. f. Kreislaufforsch.* 26: 18, 1934.
15. Wilson, F. N., Johnston, F. D., MacLeod G., and Barker, P. S.: *AM. HEART J.* 9: 447, 1934.
16. Storti, E.: *Ztschr. f. Kreislaufforsch.* 27: 830, 1935.
17. Katz, L. N., and Korey, H.: *Am. J. Physiol.* 111: 83, 1935.
18. Report of National Tuberculosis Association: *Am. Rev. Tuberc.* 6: 331, 1922.

# Department of Clinical Reports

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## THROMBO-ANGIITIS OBLITERANS IN WOMEN

### REPORT OF A CASE\*

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**T**HROMBO-ANGIITIS obliterans rarely affects women. The reason for this is obscure. In view of what is known about the relationship of smoking to thrombo-angiitis obliterans, it is easy to assume that the smaller incidence of this vascular disease among women is due to the fact that fewer women are smokers. Acceptance of this explanation would need to be based on data indicating that the ratio of the number of men smokers to women smokers approaches the ratio of the number of men with thrombo-angiitis obliterans to the number of women with this disease.

We have studied the records of 200 women between the ages of thirty and fifty years who were examined consecutively at the Mayo Clinic in 1935. Twenty-four of these women (12 per cent) smoked tobacco. In a comparable study of the records of 200 men, 140 (70 per cent) were smokers. This agrees closely with the results of Barker's study in 1931,<sup>1</sup> who found that 69.2 per cent of men were smokers. Barker's study likewise showed that, of 350 male patients with thrombo-angiitis obliterans, four, or 1.1 per cent, were nonsmokers. The ratio of men smokers to women smokers in our series of patients without thrombo-angiitis obliterans is approximately 6:1 (140 men to 24 women). This ratio is much smaller than that of men with thrombo-angiitis obliterans to women with thrombo-angiitis obliterans, which, according to various authors, is from 70:1 to 500:1. It appears, therefore, that tobacco smoking does not explain the differential sex incidence of thrombo-angiitis obliterans. The time element in smoking, however, may be important. It is probable that the women in our series had not smoked tobacco as long as had the men. If the smoking of tobacco is the sole etiological factor in thrombo-angiitis obliterans, it is safe to predict that within the next few decades many more women with thrombo-angiitis obliterans will be observed and that the ratio of women with this disease to men with the disease should approach the ratio of women smokers without thrombo-angiitis obliterans to men smokers without the disease, which is about 1:6 at the present.

Worthy of note in attempting to explain the difference in incidence of thrombo-angiitis obliterans in the sexes is the experimental work of

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McGrath.<sup>2</sup> Female rats were poisoned with ergotamine until gangrene of the tail occurred. If theelin were injected into these animals, the same amounts of ergotamine did not cause gangrene. Theelin did not, however, protect male rats from ergotamine-induced gangrene.

In 1932 Horton and Brown<sup>3</sup> collected from the literature seven cases of thrombo-angiitis obliterans affecting women, and they presented at that time ten additional cases from a series of 700 cases of thrombo-angiitis obliterans observed at the clinic. We agree with Horton and Brown that only Cases 1, 2, and 3, of those which they collected from the literature, are acceptable. Two of these three cases were reported by Buerger<sup>4</sup> in 1924, the other was reported by Meleney and Miller<sup>5</sup> in 1925. Cases reviewed by Horton and Brown which were reported earlier by Koyano,<sup>6</sup> by Telford and Stopford,<sup>7</sup> by Trabaud and Chaty,<sup>8</sup> and by Trabaud and Mredde<sup>9</sup> do not, in our opinion as well as that of Horton and Brown, fulfill the minimal requirements for the diagnosis of thrombo-angiitis obliterans. The data given by Dürk<sup>10</sup> in 1930, in his report of a case of thrombo-angiitis obliterans affecting a woman, are entirely inadequate for such a diagnosis. The case seems to have been only one of superficial phlebitis, affecting a Jewess twenty-seven years old, who used tobacco excessively. Of the ten cases reported from the clinic by Horton and Brown in 1932, in some, all of the characteristics of the disease, as it is encountered in men, were present. In 1935, Silbert<sup>11</sup> reported two cases of thrombo-angiitis obliterans affecting women. His first case, however, is an example of unilateral occlusive arterial disease suggesting arterial embolism.

The total number of cases reported as thrombo-angiitis obliterans affecting women is twenty. In several instances the authors themselves reported uncertainty regarding the diagnosis. We are adding the following case which impresses us as being unquestionably an example of thrombo-angiitis obliterans affecting a woman. This is the first case observed at the clinic since the report of Horton and Brown. In addition, two questionable cases have been observed here. During the intervening time approximately 350 cases of thrombo-angiitis obliterans have been observed.

#### REPORT OF CASE

A Scandinavian woman, forty-one years old, was admitted to the clinic in September, 1935. There was no family history of vascular disease. She had had typhoid fever at the age of four years, frequent attacks of tonsillitis until she was twenty-five, and at the age of nine years rheumatic fever, which had confined her to bed for four months. She had smoked from ten to fifteen cigarets daily for ten years prior to her admission. In the two years before admission she had noted coldness of the distal half of the left leg and of the left foot and toes. As a result of exposure to cold, the distal half of the left foot and the toes had in turn become pale, cyanotic, and red. Associated with these vasomotor disturbances

numbness and aching pain had occurred. Even getting from bed onto a cold floor induced changes in color; as a result, the patient had learned to put on her shoes before getting out of bed. In the six months prior to admission walking from four to six blocks had produced aching pain in the distal half of the left foot and calf of the left leg; this necessitated rest, which had produced relief in a few minutes. Because of such pain the patient had almost entirely discontinued walking. For a year the first toe of the right foot had been numb and at times quite cold; also, the vasomotor changes just described had involved the third finger of the left hand, which ached after exposure to ice or cold and was numb at times even without exposure. The skin of the dorsal portion of the left foot and toes had cracked and peeled a few weeks before admission.

On physical examination the patient looked well; she was 63 inches (160 cm.) tall and weighed 142 pounds (64.4 kg.). The blood pressure in millimeters of mercury was 136 systolic and 80 diastolic. General examination gave negative results except for indicating the presence of a left Horner's syndrome, which had been present since childbirth nineteen years before.

Examination of the arteries for pulsations\* revealed the following: right and left femoral and right and left popliteal, grade 4; right dorsalis pedis, 1; left dorsalis pedis, 0; right posterior tibial, 2; left posterior tibial, 0; right ulnar, 4; left ulnar, 0; right radial, 4; and left radial, 4 (Table I). The compression test devised by Allen<sup>12</sup> was positive for the left ulnar artery. Elevation of the left foot produced pallor, grade 3, and lowering caused rubor, grade 3; the color returned slowly. There was marked decrease in the angle of circulatory efficiency. An area of superficial phlebitis was present on the dorsum of the left foot.

Röntgenograms of the left foot and leg revealed a few small phleboliths at the level of the middle third of the tibia. Routine laboratory studies, including a serological test for syphilis, determination of hemoglobin, enumeration of the erythrocytes and leucocytes, and urinalysis, gave negative results. A diagnosis of thrombo-angiitis obliterans was made.

TABLE I  
PULSATIONS IN PERIPHERAL ARTERIES\*

ARTERY	RIGHT	LEFT
Femoral	4	4
Popliteal	4	4
Dorsalis pedis	1	0
Posterior tibial	2	0
Ulnar	4	0
Radial	4	4

\*4 represents normal pulsation; 0, complete absence of pulsations.

#### COMMENT

The age of onset of symptoms, the presence of rather characteristic vasomotor disturbances and typical intermittent claudication, the occlusion of the large arteries, the presence of superficial phlebitis, the absence of demonstrable sclerosis, and the apparently progressive nature of this condition, leave no doubt concerning the clinical diagnosis of thrombo-angiitis obliterans. The use of smoking tobacco is supportive evidence for the diagnosis.

\*Graded from 0 to 4; 4 denotes normal pulsations and 0 denotes complete absence of pulsations.

## REFERENCES

1. Barker, N. W.: The Tobacco Factor in Thrombo-angiitis Obliterans, *Proc. Staff Meet., Mayo Clin.* 6: 65, 1931.
2. McGrath, E. J.: Experimental Peripheral Gangrene, *J. A. M. A.* 105: 854, 1935.
3. Horton, B. T., and Brown, G. E.: Thrombo-angiitis Obliterans Among Women, *Arch. Int. Med.* 50: 884, 1932.
4. Buerger, Leo: The Circulatory Disturbances of the Extremities Including Gangrene, Vasomotor, and Trophic Disorders, Philadelphia, 1924, W. B. Saunders Company.
5. Meleney, F. L., and Miller, G. G.: A Contribution to the Study of Thrombo-angiitis Obliterans, *Ann. Surg.* 81: 976, 1925.
6. Koyano, K.: A Clinical Study of 120 Cases of Thrombo-angiitis Obliterans Among the Japanese, *Acta scholae med. univ. imp. in Kioto* 4: 489, 1921-1922.
7. Telford, E. D., and Stopford, J. S. B.: Two Cases of Thrombo-angiitis Obliterans in Women, *Brit. M. J.* 1: 1140, 1927.
8. Trabaud, J., and Chaty, Choukat: Étude microscopique des lésions dans un cas de maladie de Léo Buerger chez une femme musulmane, *Bull. et mém. Soc. méd. d. hôp. de Paris* 47: 583, 1931.
9. Trabaud, J., and Mredde: Maladie de Léo Buerger chez une jeune fille musulmane, *Bull. et mém. Soc. méd. d. hôp. de Paris* 47: 579, 1931.
10. Dürck, Hermann: Die sogenannte "Thromboangiitis obliterans" im-Rahmen der Infektiöstoxischen Gefässentzündungen, *Verhandl. d. deutsch. path. Gesellsch.* 25: 272, 1930.
11. Silbert, Samuel: Thrombo-angiitis Obliterans in Women: Report of Two Cases, *Ann. Surg.* 101: 324, 1935.
12. Allen, E. V.: Thrombo-angiitis Obliterans: Methods of Diagnosis of Chronic Occlusive Arterial Lesions Distal to the Wrist, *Am. J. M. Sc.* 178: 237, 1929.

## FATAL DIGITALIS POISONING OCCURRING IN A NORMAL INDIVIDUAL\*

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THE purpose of this report is to describe a case of fatal digitalis poisoning in a normal individual. The electrocardiogram of this patient presents alterations which will be described in detail. It is hoped that comparison of these changes with the electrocardiographic alterations resulting from therapeutic doses may be of value in preventing overdosage of digitalis.

William Withering<sup>1</sup> in 1785 reported that very large doses of digitalis caused slow pulse, green or yellow vision, convulsions, syncope, and death.

Cohn<sup>2</sup> in 1915 described electrocardiographic changes associated with digitalis therapy which developed in the T-wave in individuals with "an early rather than advanced stage of heart disease." These changes consisted of lowered amplitude of the T-waves, first in Lead III, later in Lead II. In some instances the T-waves became diphasic.

White<sup>3</sup> administered from 2.0 to 3.0 gm. of digitalis leaves to five normal young adults. The amplitude of T, especially in Lead II, was decreased, and later the P-R interval was increased.

Berger<sup>4</sup> reported a patient with mild rheumatic heart disease who received approximately 64 gm. of digitalis in a month. The patient developed nausea, vomiting, yellow vision, electrocardiographic signs of "too much digitalis" (i.e., partial A-V block, depressed S-T segments in Leads I and II), and died suddenly.

Human fatalities resulting from strophanthin are summarized by Robinson.<sup>5</sup> Sollmann<sup>6</sup> reported that 2.5 gm. taken at one dose proved fatal. Levine and Cunningham<sup>7</sup> studied digitalis toxicity in cats and concluded that the margin of safety (the difference between the percentage causing death and that responsible for the earliest evidence of toxicity) averaged 48 per cent. It must be remembered that these investigators were studying animals with normal hearts. Lewis<sup>8</sup> stated that he has seen more than one instance of avoidable death which resulted from failure to withdraw digitalis when "excessive slowing or coupling occurred." White<sup>9</sup> warns that a considerable percentage of the lethal dose has been given when the electrocardiogram reveals excessive inversion of the T-wave and S-T segment, prolongation of the P-R interval, intraventricular block, bigeminal rhythm, or ventricular tachycardia.

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Cushny<sup>10</sup> has described fully the toxic manifestations of excessive digitalis administration in animals. There was an initial rise of arterial blood pressure followed by a pronounced fall, and a variety of arrhythmias developed. Other toxic manifestations were marked depression of the respiratory center, muscular weakness, and visual disturbances, probably of central nervous system origin, and finally ventricular fibrillation was followed by marked ventricular dilatation and cardiac standstill.

#### CASE REPORT

The present report concerns a woman, thirty-one years old (Case No. 48529), who was admitted to the hospital three hours after taking the entire contents (about 300 grains) of a 6-8 oz. bottle of tincture of digitalis for suicidal purposes while acutely intoxicated.

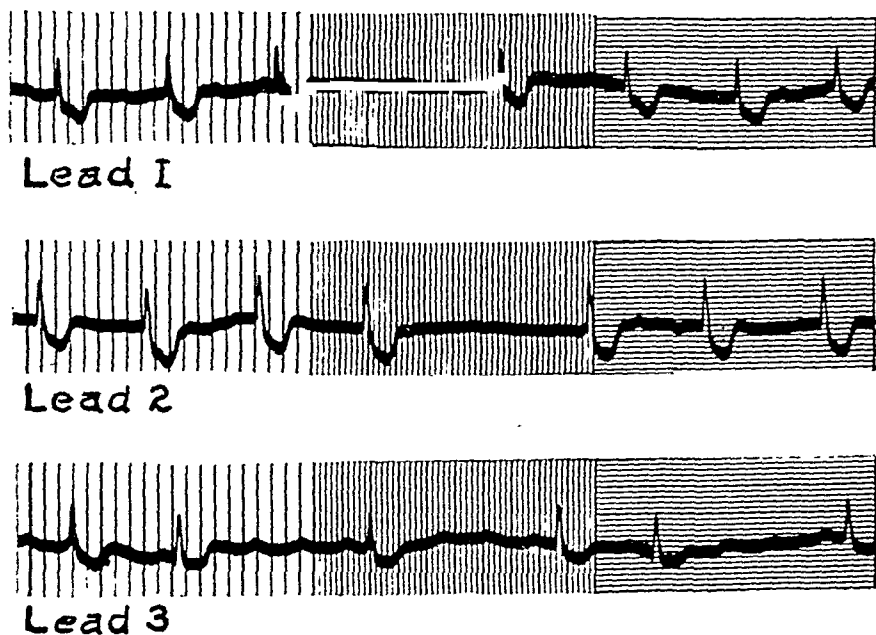


Fig. 1.—Complete A-V dissociation; auricular rate 170; ventricular rate 60 to 70; marked depression of S-T segments in Leads I and II. Inversion of T-waves.

The patient's earlier history was entirely normal. The digitalis had been recently purchased by her father who presumably had heart disease. Three hours after taking the digitalis she became nauseated, vomited a greenish material, and was brought to the hospital. Gastric lavage with tannic acid was carried out, and apomorphine, gr.  $\frac{1}{40}$ , was administered.

On admission she was semistuporous. Temperature 101.4° F. (rectal), respirations 24, pulse 124, blood pressure 120/75. The pupils were equal, regular and reacted to light and accommodation; the tongue was covered with green coating. The neck showed no venous distention. The admitting physician stated that the cardiac rhythm was absolutely regular but that there was marked variation of the intensity of the heart sounds, runs of loud beats were followed by runs of distant, muffled beats. The reflexes were diminished (alcohol?).

Nine hours later when examined by one of us the pulse was grossly irregular, and there was coincident absence of heart sounds in the absence of the radial pulse. The

heart was of normal size on percussion. No murmurs were heard. The blood pressure was 120/50. The clinical diagnosis of partial heart-block was confirmed by an electrocardiogram.

The patient continued to be nauseated and vomited frequently, remained semi-stuporous, and did not respond to stimulants (caffeine, atropine and adrenalin). The pulse disappeared in twelve hours and continued to be imperceptible. The heart sounds were distant and of varying intensity. The respirations were slow and irregular. During the twelfth hour the patient had two mild convulsive seizures; respirations ceased; cyanosis increased but heart action continued irregularly. Artificial respiration was given for five minutes; during this time the heart sounds could be heard; and the heart rate was accelerated by intracardiac adrenalin. Death occurred from respiratory failure.

Unfortunately, permission for autopsy could not be obtained.

The electrocardiogram is reproduced in Fig. 1, and shows an auricular rate of 170 with complete auriculoventricular dissociation, the ventricular rate averaging 66 per minute. The S-T segment take-off is conspicuously low in Leads I and II and is depressed in Lead III. Thus, there is no reciprocal relationship between Leads I and III as is frequently encountered in coronary occlusion. The negative T-waves are merged with the S-T segment. As the maximum effect on the T-waves usually occurs about six hours after any one dose of digitalis (Pardee<sup>11</sup>), the changes in this record are probably maximum. However, the significant and unusual change is the very low take-off of the S-T segments.

#### DISCUSSION

As far as we can ascertain, this is the first recorded electrocardiogram in fatal digitalis intoxication in a normal individual. The auricular rate of 170, with an idioventricular rate of 60 or 70 in the presence of complete heart-block, is unusual. This is of especial interest as it is generally thought that large doses of digitalis produce bradycardia.

The nausea, the vomiting, and the respiratory character of death appeared to be related to the "central" action of digitalis on the nervous system rather than to peripheral action on the heart itself. Of especial interest was the period of apparent clinical improvement four hours before death and the *modus exitus* with respiratory failure.

#### SUMMARY

Death from respiratory failure occurred in a normal individual twelve hours after the ingestion of approximately 300 grains of digitalis. Auricular tachycardia, A-V block, and marked depression of S-T segments were shown electrocardiographically.

#### REFERENCES

1. Withering, Wm.: An Account of the Foxglove and Some of Its Medical Uses, Birmingham, 1785, p. 184.
2. Cohn, A. E.: Clinical and Electrocardiographic Studies of the Action of Digitalis, J. A. M. A. 64: 463, 1915.



3. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram With Especial Reference to A-V Conduction, *J. Exper. Med.* 23: 613, 1916.
4. Berger, E. H.: Digitalis Intoxication, *Northwest Med.* 32: 195, 1933.
5. Robinson, G. S.: Therapeutic Use of Digitalis, *Medicine* 1: 38, 1922.
6. Sollmann, Torald H.: A Manual of Pharmacology and Its Application of Therapeutics and Toxicology, Philadelphia and London, 1917.
7. Levine and Cunningham: The Margin of Safety of Intravenous Digitalis in Cats, *Arch. Int. Med.* 31: 267, 1920.
8. Lewis, Sir Thomas: Diseases of the Heart, New York and London, 1933, The Macmillan Company, p. 87.
9. White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 578.
10. Cushny, A. R.: Digitalis and Its Allies, London, 1925, Longmans, Green & Co., p. 143.
11. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, 1933, Paul B. Hoeber, p. 99.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Schade, H.: The Transmission of Pulsations from Arteries to Veins and Its Bearing on the Circulation of Blood. *Ztschr. f. Kreislaufforsch.* 28: 144, 1936.

This report, compiled posthumous by O. Hepp, is based on extensive studies of animals and models. Work on models demonstrated that the efficacy of the transfer of the pulsation from arteries to veins increases as the arterial pulse amplitude and the pulse frequency are increased until optimum values are reached.

Animal experiments and roentgenological studies in man demonstrated pulsatory fluctuations in blood velocity in the peripheral veins. These were synchronous with the arterial pulse. In the presence of functionally efficient venous valves, these pulsations in the veins cause an effective acceleration of flow toward the heart. Changes in tone of the veins and in the degree of extravascular support offer an automatic regulation of the transmission of the pulsations from the arteries to the veins. Records of peripheral venous pulsations were obtained with a special sphygmograph which excluded the possibility of retrograde transmission from the heart. These peripheral venous pulses were of relatively small amplitude.

L. N. K.

Palme, F.: Action of Adrenalin on the Carotid Sinus. *Ztschr. f. Kreislaufforsch.* 28: 173, 1936.

Topical application of 1:1,000 adrenalin solution to the exposed carotid sinus of the rabbit caused a protracted hypertension.

L. N. K.

Walter, J.: Effect of Calcium on Adrenalin Reaction. *Arch. di. sc. biol.* 38: 300, 1935.

Experiments were conducted on perfusion of the isolated rabbit's ear and frog's limb. The normal calcium chloride content of the perfusing fluid was 0.2 per cent for the rabbit and 0.1 per cent for the frog. A fourfold increase in the calcium caused vasoconstriction; absence of calcium caused vasodilation; and subsequent restoration of calcium, marked vasoconstriction. A decrease in the calcium reduced the normal vasoconstrictor response to adrenalin (1 to 10 million for the rabbit, 1 to 5 million for the frog). Increased calcium content had a different effect in the two cases.

E. A.

Smith, Dietrich C., and Mulder, Arthur G.: The Effect of Accelerator Nerve Stimulation and of Adrenalin on Recovery From Ventricular Fibrillation in the Cat. *Am. J. Physiol.* 115: 507, 1936.

In cats spontaneous recovery from ventricular fibrillation following faradization of the ventricles occurs in the large majority of animals.

Evidence is presented to show that the time of fibrillation varies directly with the weight of the cat (size of the heart).

Stimulation of the accelerator nerves during ventricular fibrillation in the cat shortens the duration of the fibrillation.

While the heart is under the influence of adrenalin, recovery from fibrillation following faradization of the ventricles is instantaneous.

AUTHOR.

Nicolai, L., and Hantschmann, L.: On the Stereostethoscope. *Klin. Wehnschr.* 15: 91, 1936.

The stereostethoscope differs from the common model in that it has two stethoscope receivers, one leading to each ear. In ausculting murmurs which are difficult to locate, the relative intensity of the murmur heard in each ear gives an idea of the place of origin of the sound. Clinical trial with heart murmurs and pulmonary râles have proved useful in helping to locate the origin of these sounds.

R. K.

Duomarco, J.: Relationship of Mean Arterial and Intraventricular Pressure to Cardiac Output. *Compt. rend. Soc. de biol.* 121: 553, 1936.

The ratio of the intraventricular mean pressure to the mean arterial pressure is a criterion of cardiac efficiency. When this value is greater than 0.5, it may be due to limitation of ventricular distention by pericardium, by excesses of work, or by injury.

E. A.

Sigler, Louis H.: Further Observations on the Carotid Sinus Reflex. *Ann. Int. Med.* 9: 1380, 1936.

Slowing of the heart induced by the carotid sinus reflex was studied in 426 cases, which were divided into seven groups: (1) arteriosclerotic heart disease; (2) hypertension and hypertensive heart disease; (3) arteriosclerotic and hypertensive heart disease; (4) rheumatic heart disease; (5) psychoneurotic heart disease; (6) other forms of heart disease or disturbances; and (7) general constitutional disturbances. Various conditions arranged in order of greatest frequency and degree of slowing induced by the carotid sinus reflex follow: arteriosclerotic and hypertensive heart disease, rheumatic heart disease, general constitutional disease, psychoneurotic and miscellaneous heart disease. Hypertension seems to increase the frequency but diminish the degree of the carotid sinus reflex. The cardio-inhibitory reflex appears to depend on a constitutional vagotonic tendency, which is more marked among males and develops with advancing age. General toxic or irritative states, endocrine factors, intracarotid blood pressure, and local disease, or disturbances in the heart itself seem to play a part in sensitizing the reflex.

AUTHOR.

Wright, Irving S., and Lilienfeld, Alfred: The Pharmacological and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid) With Especial Reference to Its Effects on the Capillary Fragility. *Arch. Int. Med.* 37: 241, 1936.

After a preliminary review of the nature and properties of crystalline vitamin C (cevitamic acid), with a brief discussion of some of the therapeutic claims made for the substance, the authors give their experience with cevitamic acid, particularly in the treatment of certain of the hemorrhagic diseases. As an aid to the diagnosis of vitamin C malnutrition, the authors describe a capillary fragility test which is a modification of the tourniquet test performed under standard conditions. With

this technic a normal result shows not more than ten petechiae within a delimited area of skin. Ten to twenty is a marginal zone, and a count above twenty appears to be definitely abnormal.

The authors feel that a history of scanty vitamin C intake, together with an increased capillary fragility, which decreases definitely on the administration of vitamin C, is fair presumptive evidence of vitamin C malnutrition. Cevitamic acid was found to be of great value in clinical and "subclinical" scurvy, and apparently of no value in thrombocytopenic purpura and hemophilia.

AUTHOR.

**Kayser, G., and Weber, A.: Registration of Heart Sounds and Their Reproduction by Means of the Phototone Technic.** *Munchen. med. Wehnschr.* 82: 1032, 1935.

Heart sounds are recorded on moving film by means of a microphone. They can be reproduced by running the film past a photoelectric cell which is connected through an amplifier with a loud-speaker or ear phone. This method is valuable for teaching purposes and permits the combination of auditory and visual examination of the heart sounds. When the sounds are recorded simultaneously with the electrocardiogram, it permits better timing of murmurs, a clearer interpretation of the type of third heart sound or gallop rhythm present. A visual record picks up low pitched sounds which the ear may not hear.

L. N. K.

**Pereira, J. C.: Phonocardiographic Studies in 50 Normal Pregnancies.** *Rev. argent de cardiol.* 2: 323, 1935.

The heart sounds (Wiggers and Dean), the venous pulse (Frank) and the electrocardiogram (D 1) were simultaneously recorded in fifty normal pregnant women. The heart rate, duration of systole, and systolic-diastolic relation were found to show no significant differences as compared with those found in young male adults. In  $62 \pm 4.6$  per cent of the cases only the first and second sounds were recorded; in  $22 \pm 3.98$  per cent the first, second, and third sounds were recorded; in  $10 \pm 2.85$  per cent the auricular, first, second, and third sounds were present in the records and in  $6 \pm 2.2$  per cent the auricular, first, and second sounds were recorded.

Comparing these data with those gathered by Braun Menendez and Orias in healthy male young adults, it becomes apparent that the third normal sound is less frequently recorded in normal pregnant women while the auricular sound is recorded with about the same frequency. No reduplication of either the first or second sound was recorded. In two cases in which direct auscultation indicated a reduplication of the second sound, a third physiological sound was recorded.

AUTHOR.

**Snellen, H. A.: Conduction Disturbances in the Auricles.** *Ztschr. f. Kreislaufforsch.* 28: 234, 1936.

A case is described of a forty-two-year-old woman with marked congestive failure, in whose electrocardiogram extra waves were present interspersed among the regular PQRST waves. These extra waves occurred at a regular slow, constant rate (about 45 per minute). The author interprets these waves as originating in an auricular pacemaker which controls a region of the auricles blocked off from the rest of the auricles and from the ventricles. At autopsy the right ventricle was found dilated and hypertrophied. However, the coronary arteries, the auricles, and the myocardium were found to be normal.

L. N. K.

Tigges, Franz: The Electrocardiogram in Anoxemia. *Ztschr. f. Kreislaufforsch.* 28: 225, 1936.

This report deals with a study of (1) the effect of placing fifteen normal persons in low pressure chambers and reducing the pressure in the chamber to an equivalent of 5,000 to 7,000 meters above sea level, (2) the effect of reducing the content of O<sub>2</sub> in inspired air to as low as 8 per cent in thirteen experiments on normal persons, and (3) the effect of inhalation of pure oxygen in six experiments with cyanotic patients.

Anoxemia, sufficient to produce mountain sickness, caused acceleration of heart rate, shortening of the P-R and QRST intervals, augmentation in the size of the P-wave, and flattening of the T-wave. On relieving the anoxemia, the deviations were restored to and temporarily beyond the normal values. No particular electrocardiographic changes marked the onset of mountain sickness. Oxygen inhalation in cyanotic patients caused changes the reverse of those seen in normal individuals rendered anoxic.

L. N. K.

Hinrichs, Alfred: The Differential Diagnosis of A-V Nodal Rhythm. *Ztschr. f. Kreislaufforsch.* 28: 205, 1936.

This is a case report of a thyrotoxic patient having a tonsillar abscess, who developed an incomplete A-V block with Wenckebach periods. The next day he had a regular rhythm with a rate about 110 beats per minute. The P-wave followed the QRS complex by about 0.20 sec. simulating (A-V) nodal rhythm. Analysis showed, however, that this was in reality a sinus tachycardia with a markedly prolonged P-R interval.

L. N. K.

Koch, Eb.: A Scheme for Electrocardiography. *Ztschr. f. Kreislaufforsch.* 28: 200, 1936.

A chart is presented showing the lines of equipotential in a circular electrical field having widely separated large poles in the center. A second circular chart is given of the same diameter, which has three lines radiating from the center at an angle of 120 degrees from each other. When the second chart is superimposed on the first, it will give the values of the potential at the three electrodes and in the three leads correctly in any position. The angle  $\alpha$  can also be obtained. The author claims that this procedure is accurate, unlike the trigonometric solution of the Einthoven triangle. The author has not yet made the correction in the case of an eccentrically located bipole.

L. N. K.

Neslin, W.: Autonomic Auricular Rhythm. *Wien. Arch. f. inn. Med.* 28: 243, 1936.

The author reports a case in which sinus rhythm coexisted with rhythm discharge from another focus in the auricles. The patient, fifty-three years old, manifested definite evidence of cardiac failure. The electrocardiogram showed sinus arrhythmia, ventricular premature beats, and evidence of intraventricular block. In addition, small waves occurred at regular intervals at a rate of thirty per minute and were not followed by ventricular complexes. They bore no constant time relation to the normal P-waves or the QRS complexes. These regularly recurring waves are interpreted as extrasystolic P-waves arising in a rhythmic focus in the auricles. This focus and the sinus pacemaker acted independently

and each controlled its own portion of the auricles, the two regions being shielded from each other by a region of transient intra-auricular block. The sinus impulse spread to the ventricle, the other did not. The auricles, in this way, were divided into two functionally independent parts.

W. B.

Hadorn, Von W., and Tillmann, A.: Contusion of the Heart. *Ztschr. f. Kreislaufforsch.* 28: 185, 1936.

The authors present a case report of a thirteen-year-old girl who, following a severe blow of the chest, developed shock, pain in the upper abdomen, tachycardia, extrasystoles, leucocytosis, transitory S-T and T-wave abnormalities in the electrocardiogram, and an increase in sedimentation rate. This picture following chest injury should lead to the suspicion of contusion of the heart.

L. N. K.

Harrison, T. R., Friedman, Ben, and Resnik, Harry: Mechanism of Acute Experimental Heart Failure. *Arch. Int. Med.* 57: 927, 1936.

A method has been described for measuring the coronary blood flow of the dog by means of a cannula passed through the right external jugular vein into the coronary sinus. With this procedure it is possible to calculate the consumption of oxygen and the mechanical efficiency of the heart under various conditions. The sources of error involved have been discussed.

Values are reported for the coronary blood flow and for the work, oxygen consumption, and mechanical efficiency of the hearts of morphinized dogs subjected to no surgical procedure other than the insertion of arterial and venous cannulas. The amount of oxygen consumed by the heart was in general about 10 per cent of that used by the body as a whole. The average value for the mechanical efficiency of the heart was 17 per cent.

An increase in work produced either by increasing the cardiac output or by raising the blood pressure caused an increase in the mechanical efficiency of the heart.

Heart failure produced by chloroform was associated with a decline in arterial blood pressure, in oxygen consumption and in cardiac output. The proportion of the oxygen absorbed by the heart increased, and the mechanical efficiency of the heart diminished. The systemic venous pressure rose only when the animal was moribund. The cardiac output in proportion to the metabolism underwent no constant changes. At autopsy the heart was observed to be dilated, and the lungs were edematous.

Heart failure produced by potassium chloride was associated with a rise in systemic venous pressure, but edema of the lungs did not develop. Constant alterations in the arterial blood pressure, cardiac output, and arteriovenous oxygen difference were not noted. The cardiac consumption of oxygen increased, and the mechanical efficiency of the heart diminished. Dilatation of the heart was a constant post-mortem observation.

The observations support the validity of the backward failure (back pressure) theory of the mechanism of heart failure. They are not in accord with the forward failure (diminished output) hypothesis. They demonstrate that in the intact animal, as in the heart-lung preparation, heart failure is characterized by an increase in the volume of the heart and a decrease in the mechanical efficiency.

AUTHOR.

Talley, James E., and Fowler, Kenneth: Tetralogy of Fallot (Eisemenger Type) With Hypoplasia of the Dextroposed Aorta. *Am. J. M. Sc.* 191: 618, 1936.

The patient, a woman a little over thirty-one when she died, was born at eight months and was a "blue baby." She had a normal physical and mental develop-

ment, passed through two pregnancies and was able to take care of her house until within a month of her death. The diagnosis of tetralogy of Fallot, with the incompetency of the pulmonary valves, was confirmed post mortem. In addition there was a hypoplasia of both the thoracic and abdominal aorta, which was not suspected.

AUTHOR.

**Baker, Thomas, and Shelden, Walter D.:** Coarctation of the Aorta With Intermittent Leakage of a Congenital Cerebral Aneurysm. Report of a Case. *Am. J. M. Sc.* 191: 626, 1936.

A series of an unusually large number of consecutive necropsies indicates that coarctation of the aorta occurs far more frequently than is clinically appreciated. The pathology and diagnosis of this anomaly is discussed and attention is called to the ease with which this diagnosis may be confirmed or denied. The association of congenital cerebral aneurysm with coarctation is emphasized. A case in which coarctation with possible intermittent leakage of a congenital cerebral aneurysm affected a young woman still living is reported.

AUTHOR.

**Leary, Timothy:** Atherosclerosis. *Arch. Path.* 21: 419, 1936.

All the lesions of aortic atherosclerosis, save the earliest mucoid change, are due to the presence of cholesterol. They are primarily intimal and depend for their nutrition on imbibition through the endothelium. Variation in the character of these lesions is determined by the age of the subject and of the lesions.

In youth cholesterol is introduced into the subendothelial tissue of the intima by globular lipophages or is engulfed by globular lipophages in this situation. Young fibroblastic tissue is produced in the subendothelial tissue, and the young fibroblasts engulf and metabolize the lipid, leading to its disappearance from the lesions. Repair with minimal scarring follows since the young fibroblastic tissue does not form collagen.

In middle age, cholesterol metabolism within lipid cells is slowed, the connective tissue forms collagen and scar tissue is produced. There is interference with imbibition of nutriment through the scar tissue, and the deep layers undergo necrosis, with the formation of secondary atheromatous "abscesses" (atherocheumas). Scars are the typical lesions in this period.

In old age, cholesterol metabolism ceases, globular lipophages accumulate in masses, with inadequate nutrition and support, and a primary atheromatous "abscess" (atherocheuma) is the typical lesion.

The lesions of the ascending arch are exceptions to these rules, the metabolism of cholesterol being successfully carried on, as in youth, up to advanced ages. The connective tissue which is formed is reticular, as in youth, and minimal scarring is usual.

Calcification arises in connection with necrobiosis or after necrosis has developed. It is a terminal monumental deposit marking the sites formerly occupied by living tissue.

AUTHOR.

**Leary, Timothy:** Atherosclerosis. Etiology. *Arch. Path.* 21: 459, 1936.

The evidence against cholesterol as etiologic agent is considered first and is found wanting. Leary then, after considering his own and others' evidence for this substance, concludes that the disease atherosclerosis is due to disturbances of cholesterol metabolism. Stresses appear to determine the localization of the lesions.

L. H. H.

Darley, Ward, and Doan, Charles A.: Primary Pulmonary Arteriosclerosis With Polycythemia: Associated With the Chronic Ingestion of Abnormally Large Quantities of Sodium Chlorid (Halophagia). *Am. J. M. Sc.* 191: 633, 1936.

The case herewith presented is that of a young female, aged twenty years, who since early childhood had manifested the signs and symptoms of obstruction in the lesser circulation. Autopsy revealed marked pulmonary arteriolar sclerosis, dilatation of the pulmonary artery, and right ventricular hypertrophy.

During most of her life the patient had ingested abnormally large amounts of salt (as much as 3 pounds in one week). No cause for this abnormality could be found. It is of interest that her taste threshold for salt was much lower than the thresholds of persons who were normal in respect to salt desire and intake, that her fluid intake and output were not materially disturbed by variations in salt intake, and that the osmotic pressure and the chemistry of the blood were not altered.

The case is discussed at length from the standpoint of possible causes of arteriosclerosis. Moschcowitz insists that, save with very few exceptions, pulmonary arteriosclerosis is the result of long-standing hypertension in the lesser circulation. Most such cases of hypertension are secondary to congenital abnormalities of the heart or pulmonary vessels or to extravascular or intravascular circulatory obstruction. In this patient we were unable to demonstrate any cause of obstruction or hypertension in the lesser circulation other than the arteriolar hyperplasia itself. Consequently, we consider this case to be one of primary pulmonary arteriosclerosis, and, since microscopic examination of the pulmonary tissue failed to reveal any evidence of syphilitic arteritis, we feel that it should be further classified as one of unknown etiology.

AUTHOR.

Levin, Paul M., and Bucy, Paul C.: Proliferative Endophlebitis (Phleboscclerosis). Report of a Case. *Arch. Int. Med.* 57: 787, 1936.

A case of proliferative endophlebitis is presented, which appears to be unique in that the lesions were associated with symptoms definitely indicative of impairment of the venous return.

AUTHOR.

Bitzer, E. W. Observations on the Effect of Sudden Changes in Arterial Tension in Angina Pectoris. *Ann. Int. Med.* 9: 1120, 1936.

Sixty-four patients with angina pectoris were subjected to the cold pressor test. Thirty-two cases had normal blood pressures; 27 were hypertensive and five were hypotensive. Fifty-three per cent of the angina pectoris cases with normal blood pressure had a ceiling, or maximal rise, in systolic pressure to 150 mm. or more. The average rise in this group was 29.84 mm. systolic and 16.53 mm. diastolic. The greatest reaction occurred in a hypertensive case, 82 mm. systolic and 45 mm. diastolic. Two cases showed a reverse reaction, a precipitate drop in pressure, with a slowing of the pulse rate, pallor, and sweating about the head.

Electrocardiographic studies were made. A chest lead was taken immediately preceding the test and repeated at the height of the reaction. Twelve cases showed more than 1 mm. change in the QRS and T deflections during the cold pressor test. Four cases showed changes in the R-T segment.

Only one case developed an attack of angina pectoris. This individual was acutely reactive to cold. Handling ice or drinking ice water would immediately precipitate an attack, which could be relieved by immersing the hands in hot water. The carbon dioxide test was used on this patient and caused a similar rise in blood pressure but failed to produce an attack of angina pectoris.

AUTHOR.



Pinkston, J. O., Partington, P. F., and Rosenblueth, A.: A Further Study of Reflex Changes of Blood Pressure in Completely Sympathectomized Animals. *Am. J. Physiol.* 115: 711, 1936.

Completely sympathectomized and vagotomized cats and dogs were studied. Reflex rises and falls of blood pressure were obtained on stimulation of afferent nerves and these responses were not abolished by exclusion of the splanchnic vascular area. No significant reflex rises of blood pressure were obtained on occlusion of the innervated carotids. Struggle was attended by a sharp, severe fall of blood pressure in cats but not in dogs. These reactions are at least partly controlled by non-sympathetic vasomotor nerves, which are probably the dorsal root dilators.

E. A.

Albrecht, H.: Pregnancy in Essential Hypertension. *Monatschr. f. Geburtsh. u. Gynäk.* 100: 301, 1935.

Pregnancy may aggravate the conditions of the blood vessels in essential hypertension and, also, may lead to nephrosis or eclampsia. These patients, therefore, should be carefully watched.

L. N. K.

Morlock, Carl G., and Horton, Bayard T.: Variations in Systolic Blood Pressure in Renal Tumor: A Study of 491 Cases. *Am. J. M. Sc.* 191: 647, 1936.

This analysis shows striking uniformity of the readings of systolic blood pressure for the various histological types of renal tumor. Practically identical incidences for the different groups of blood pressure occurred both in cases of hypernephroma and in those of renal tumors of other types. No consistent alteration in blood pressure occurred following removal of a tumor of either type. This was particularly significant in cases of hypernephroma in which for both males and females as high an incidence of hypertension occurred after removal of the tumor as existed prior to operation. Scrutiny of the males with renal tumors other than hypernephroma would lead one to think that they experienced a diminution of arterial tension following operation, but since an exactly opposite situation existed with respect to the females, we can hardly attach significance to this. In conclusion, we found no constant increase in the blood pressure of patients who were suffering from renal tumors. In particular we failed to substantiate the observation of previous investigators: that a marked fall of an antecedent hypertension followed removal of a hypernephroma. Finally, we would suggest that this study offers clinical evidence that an epinephrine-like pressor substance is not produced by the hypernephromatous type of renal tumor.

AUTHOR.

Barker, Nelson W., and Camp, John D.: Direct Venography in Obstructive Lesions of the Veins. *Am. J. Roentgenol.* 35: 485, 1936.

The value of direct venography in obstructive lesions of the veins can be summarized as follows: (1) It may aid in evaluation of disturbances in rate of venous blood flow. (2) It may aid in localizing and determining the extent of an obstructive lesion. (3) It may be of diagnostic aid in obscure cases, particularly when extrinsic obstruction is suspected. The simplicity and safety of the method recommend it. Contraindications are idiosyncrasy to iodides and recent acute thrombophlebitis. The method has definite limitations, but there also are many possibilities for variations, and improvements in technic.

E. A.

Yater, W. M., and Cahill, J. A.: Bilateral Gangrene of Feet Due to Ergotamine Tartrate Used for Pruritus of Jaundice. J. A. M. A. 106: 1625, 1936.

This case report begins with a review in summary of the literature regarding gangrene of the extremities following therapeutic use of ergot preparations. In the present instance the gangrene ensued rapidly upon the dosage of 0.5 mg. ergotamine tartrate hypodermically for six and one-third days. Arteriograms showed a complete occlusion of the main arteries of the leg in the lower one-third. Both lower legs were amputated.

A pathological report of the vessels in the amputated portions is included. The lesion is essentially one of intense arterial constriction, with varying amounts of hyaline degeneration in the vessel walls.

L. H. H.

Gould, S. E., Price, A. E., and Ginsberg, H.: Gangrene and Death Following Ergotamine Tartrate (Gynergen) Therapy. J. A. M. A. 106: 1631, 1936.

A case report of gangrene of both lower legs, and intense peripheral artery involvement in other parts of the body following the subcutaneous injection of four daily doses of ergotamine tartrate totaling 1 mg. The patient died within a day after the last of the four doses had been given.

The drug had been administered as treatment for the pruritus of jaundice following neoarsphenamine therapy. Post-mortem examination showed all the arterioles examined to be contracted.

L. H. H.

Cole, Harold N., and Usilton, Lida J.: Cooperative Clinical Studies in the Treatment of Syphilis. I. Uncomplicated Syphilitic Aortitis: Its Symptomatology, Diagnosis, Progression, and Treatment. Arch. Int. Med. 57: 893, 1936.

The frequency of incidence of uncomplicated syphilitic aortitis is 4.9 per cent in patients admitted to the clinic with latent syphilis or syphilis in the late stage (exclusive of benign late syphilis of the bones or skin and syphilis of the viscera other than the cardiovascular organs). The total number of patients with uncomplicated syphilitic aortitis was 326. The manifestation was observed nearly three times more frequently in negroes than in white patients.

Ten per cent of the patients in whom uncomplicated syphilitic aortitis was detected had had the infection for less than five years.

The Wassermann reaction of the blood was positive in 72 per cent of the cases. There were unquestionable abnormalities of the spinal fluid in 49 per cent of the cases in which examination was made.

Of 935 patients with the early stage of syphilis followed for a period of from three to ten years, cardiovascular syphilis developed in 1.6 per cent; among 105 patients followed for from ten to twenty years, cardiovascular syphilis developed in 6.7 per cent. However, among the patients who were followed from three to twenty years, none of the graver forms of cardiovascular syphilis developed if treatment had been adequate and regular during the early stages of syphilis.

It was noted that treatment definitely improved the outlook in 267 patients followed for one year or more after the detection of uncomplicated syphilitic aortitis.

The average duration of life in patients who died has been increased from thirty-four to eighty-five months when adequate treatment has been given after the detection of uncomplicated syphilitic aortitis.

Of patients adequately treated after the detection of uncomplicated syphilitic aortitis, 63 per cent were living and free from symptoms, with no progression of the

cardiovascular syphilis, as compared with 49 per cent of those inadequately treated.

Cardiovascular syphilis was definitely or probably the cause of death in 7.9 per cent of the patients inadequately treated after the detection of uncomplicated syphilitic aortitis, as compared with 2.4 per cent of those adequately treated.

The average duration of life for patients who had been treated with small doses of arsenicals was twenty months longer than that for patients who had been treated with large doses.

In cases of uncomplicated syphilitic aortitis it is well to give a preliminary course of injections of a soluble or an insoluble preparation of heavy metal.

AUTHOR.

Cole, Harold N., and Usilton, Lida J.: Cooperative Clinical Studies in the Treatment of Syphilis: Cardiovascular Syphilis. II. Syphilitic Aortic Regurgitation: Its Treatment and Outcome. *Arch. Int. Med.* 57: 910, 1936.

There were 260 cases of syphilitic aortic regurgitation in the entire group of cases of cardiovascular syphilis. Two hundred and fifty-seven patients were admitted with latent syphilis or syphilis in the late stage (principally with involvement of the cardiovascular or the central nervous system), and an additional 3 patients admitted with syphilis in the early stage were detected during treatment in these clinics.

The frequency of aortic regurgitation in patients who had been under observation or treatment for six months or longer and who were admitted with syphilis in the late stage (principally with involvement of the cardiovascular or central nervous system) or with latent syphilis was 4.1 per cent.

Aortic regurgitation was observed twice as frequently in the negro as in the white patients; the incidence was more than three times higher in negro men than in white men.

Aortic regurgitation was observed most frequently from twenty to thirty years after infection.

The Wassermann reaction of the blood showed some degree of positivity in 85 per cent of the cases in which the test was carried out within ten days of the detection of aortic regurgitation.

In the cases in which a lumbar puncture was done, the spinal fluid of 82, or 62 per cent, showed definite abnormalities.

One of the most interesting facts revealed from these data is that 69 per cent of the patients had had no antisyphilitic treatment prior to that given for aortic regurgitation.

The treatment administered to certain patients who apparently received adequate therapy before the appearance of the aortic regurgitation was found to have been irregularly given after the syphilis was in the late stages.

The average duration of life was increased from forty to fifty-five months with adequate treatment after the detection of the syphilitic aortic regurgitation.

The administration of an adequate amount of both an arsenical and a heavy metal was found to be highly beneficial to patients with syphilitic aortic regurgitation.

From the patients with syphilitic aortic regurgitation or aneurysm who died, the average duration of life was thirty months when congestive heart failure was present before treatment and forty-seven months when congestive heart failure was not present.

Cardiovascular syphilis was the cause of death in 33 per cent of the patients in whom congestive heart failure had been present at some time and in 5 per cent of those in whom it had never been present.

Symptomatic relief was noted in 30 per cent of the patients who had received less than thirteen injections of an arsenical, with an interim course of a heavy metal,

and in 60 per cent of the patients who had received thirteen or more injections of an arsenical, with an interim course of a heavy metal.

A scheme of treatment for use in cases of aortic regurgitation is given.

AUTHOR.

Cole, H. N., and Usilton, Lida J.: Cooperative Clinical Studies in the Treatment of Syphilis: Cardiovascular Syphilis. III. Aneurysm: Its Symptomatology, Diagnosis, Treatment, and Outcome. *Arch. Int. Med.* 57: 919, 1936.

Seventy-four cases of sacculated aneurysm were included in the study.

In 50 per cent of the cases a saccular aneurysm was observed in the period from fifteen to twenty-five years after the infection, and in three cases, as late as from thirty-five to forty years after infection.

The location of the aneurysm is given in the text. Three patients had three aneurysms each.

The Wassermann reaction of the blood was positive in 90 per cent of the cases in which it was made within ten days of the diagnosis, and in 64 per cent of the cases in which lumbar puncture was made within two months of the diagnosis, there was a definitely abnormal fluid.

Of the total number of patients with aneurysm, 31 per cent showed concomitant involvement of the central nervous system, principally of the parenchymatous type. This percentage represents the minimum, since in a number of cases the gravity of the cardiovascular syphilis precluded the making of a lumbar puncture.

Seventy-seven per cent of the patients had not been treated prior to the detection of the aneurysm.

Of a group of 64 patients with aneurysms, with symptoms on admission, symptomatic relief was obtained in 44 per cent. Symptomatic relief was obtained in 43 per cent of the patients who were not given arsenical therapy as a part of the treatment but who did receive a good course of a heavy metal and potassium iodide, whereas symptomatic relief was gained in 30 per cent of the patients who were given less than thirteen arsenical injections and an interim course of a heavy metal; in 56 per cent of the patients who were given thirteen or more arsenical injections, with an interim course of a heavy metal, symptomatic response was obtained. In all cases comparable forms of medical cardiac regimen were used, regardless of whether antisyphilitic treatment was administered.

Of the seventy-four patients with a saccular aneurysm, 80 per cent were followed for a period of one year or longer after the detection of this involvement, 30 per cent for five years or longer, and 16 per cent for eight years or longer.

The average duration of life after the detection of the aneurysm of patients receiving an adequate amount of each drug was thirty-seven months, which increased to seventy-five months when adequate antisyphilitic treatment was given.

Among the twenty-two patients who died, there were thirteen who died definitely or presumably of cardiovascular syphilis.

An outline of treatment for patients with aneurysm is suggested.

AUTHOR.

Patterson, Russel H., and Stainsby, Wendell J.: The Therapeutic Effects Following Interruption of the Sympathetic Nerves; Report on the Alcohol Block in Certain Arthritic and Vascular Cases. *Ann. Surg.* 103: 514, 1936.

Diseases definitely benefited by interrupting the sympathetic nerves are: Raynaud's disease, thrombo-angiitis obliterans, scleroderma, cardiac and aortic pain, and megacolon. The diagnostic procaine block should always be done before an attempt is made to interrupt the sympathetic nerves permanently. Blocking the

sympathetic nerves with alcohol seems to be an excellent substitute for operative procedures, but the technic of blocking should be carried out only after acquiring a thorough knowledge of the anatomy and physiology of the autonomic nervous system and after many trials on cadavers. With the present technic, it is impossible to interrupt all sympathetic nerves to an extremity without interrupting sympathetic nerves to other parts of the body, e.g., blocking the sympathetic nerves to the arm produces Horner's syndrome and also blocks some of the sympathetic pathways to the chest.

E. A.

Plá, Juan Carlos, and Cuoco, Jose A.: Embolism of the Abdominal Aorta. *Rev. argent. de cardiol.* 2: 274, 1935.

A case is reported of embolism of the abdominal aorta diagnosed clinically and confirmed by autopsy. The patient was a poorly treated syphilitic, affected also by mitral stenosis and auricular fibrillation. The embolus probably came from the left auricle in which the autopsy showed an organized thrombosis, the lower portion of which appeared irregular and torn off. The diagnosis was established on the basis of the sudden paraplegia with bilateral anesthesia and total absence of arterial pulsation in both lower limbs.

H. McC

Clute, Howard M.: Acute Arterial Obstruction from Arteritis. *New England J. Med.* 214: 137, 1936.

From the experience gained in these two cases reported, it appears that resection of part of an occluded artery, as Leriche suggests, has a beneficial effect both on the trophic disturbances in the limb and the establishment of a collateral circulation. Probably the increase in the blood supply following arteriectomy is due to paralysis of the vasomotor nerves to the accessory arteries of the heart. Excellent collateral circulation usually follows a dissection of major arteries in dogs, but gangrene frequently follows simple ligation of the same vessels. Leriche recommends dissection of the obliterated artery for certain painful amputation stumps when the vessels were ligated in continuity, for trophic ulcers on amputation stumps, and for localized arteritis and recent thrombosis in arteriosclerosis. He believes the best results occur when the entire obliterated portion of the artery can be removed, but he does not recommend the procedure in Buerger's disease.

The operative procedure in each of the cases was limited to the removal of but a short piece (2 inches) of the thrombosed vessel. No attempt was made to remove the entire artery. Such a procedure does not seem wise, first, because it does not appear necessary for good results, and, second, because such an extensive dissection might well injure some of the collateral arteries. The end-results in the first case were not so good as in the second case because of the delay in recognition of the condition until the process had advanced well up the brachial artery to involve more of the main arterial trunk. Early interference in the second case gave a better opportunity for the development of a good collateral circulation.

One must be impressed in these two cases with the apparent relation of the sympathetic nerves of a main artery to many of the symptoms and signs which follow its occlusion. From the experience gained, it appears that resection of part of an occluded arterial trunk aids in the establishment of a collateral circulation and overcomes the symptoms arising from the stimulation of the sympathetic nerves of a diseased artery.

AUTHOR.

Capps, Richard B.: A Method for Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand With the Results in Normal and Diseased States. *J. Clin. Investigation* 15: 229, 1936.

A method has been presented for measuring the tone of the veins, venules, and capillaries of the human hand as a whole and for determining the reflex reaction of these vessels to a noxious stimulus, a pinch.

It has been shown that the tone of these vessels normally increases with cold and reflexly increases with the pinch. Their tone decreases with local heat and reflexly with heat to the leg.

Evidence has been presented that the decrease in hand volume following a pinch is actually due chiefly to a reflex constriction of the veins, venules, and capillaries.

In two cases of acrocyanosis an abnormal absence of tone of the veins, venules, and capillaries has been found. Coupled with an unusually slow blood flow at low temperature, this finding can explain the clinical picture.

In two cases of severe malignant hypertension, no significant abnormalities were found by this technic.

AUTHOR.

Loman, Julius, and Myerson, Abraham: Visualization of the Cerebral Vessels by Direct Intracarotid Injection of Thorium Dioxide (Thorotrast). *Am. J. Roentgenol.* 35: 188, 1936.

The best position for puncture of the carotid artery is the supine with the head hyperextended. In this position the muscles and tissues of the neck are firmly fixed so that the artery may be entered with the least difficulty. The artery is punctured by a number 18 or 19 gauge needle at the level of the cricoid cartilage after initial cleansings of the skin and infiltration of the area with novocaine. When it is apparent beyond a doubt that the needle is within the lumen of the common carotid artery, thorotrast is injected as rapidly as possible while an assistant slows the rate of blood flow through the brain by compressing the homolateral carotid or both internal jugulars. First roentgenographic exposure is made immediately at the completion of the injection and excellent arteriograms are obtained. A fair phlebogram may be obtained by exposing a second film three or four seconds after the first one. In thirty cases no immediate or untoward effects were noted over a period of five months.

It seems probable that in selected cases direct intra-arterial injections of thorotrast will be of definite aid in the diagnosis of certain cerebral conditions, particularly neoplasms and abnormalities of the cerebral vascular tree.

E. A.

Pietrusky: The Question of Vasomotor Disturbances of the Extremities After Electrical Injuries. *Deutsch. Gerichtl. Med.* 25: 197, 1935.

Most changes in the tissues in death due to electrical injuries can be accounted for as the effects of the electricity on the vessels, such as edema, dilation of the vessels, and localized angiospasm. The dissection of bodies when death was caused by electrical injuries would appear to prove that death is due to a concentration of all the blood in the paralyzed capillary and venous system. An interesting case occurred recently where a patient touching a highly charged electric wire with the right hand received burns on both hands as the current was discharged through the left hand. The injuries healed rapidly, but several months later upon the arrival of cold weather vasomotor disturbances occurred in both upper extremities. It would seem that there is a close connection between an electric injury and disturbed circulation.

J. K.

**Battistini, Gaspare:** Clinical and Etiopathological Studies of Cyanosis, Particularly in regard to Endocrine and Constitutional Factors. *Policlinico (sez. med.)* 42: 480, 1935.

Two sisters developed acrocyanosis at the change of life. The disturbed function of the ovary in connection with a specific constitutional background is responsible for these vasomotor syndromes. Successful hormone therapy seems to prove this theory.

J. K.

**McKelvey, G. J.:** An Improved Cuff for Use with the Passive Vascular Exercise Unit. *J. A. M. A.* 106: 920, 1936.

McKelvey describes a series of soft rubber cuffs for adaptation to various sized thighs, with separate leaves which are compressed on the thigh alternately in the two phases of suction and pressure. They are attached separately to the open end of the boot and to the thigh at the start of each treatment and are claimed to cause no venous congestion.

L. H. H.

**Conway, J. H.:** Obliterative Vascular Disease. Report of Fifty-One Cases Treated With Passive Vascular Exercise. *J. A. M. A.* 106: 1153, 1936.

In this study of the clinical application of alternate suction and pressure in patients, the author states his belief that gradual pressure changes are equally effective with sudden alternation in environmental pressure and that they are without danger of injury to the intima of diseased vessels.

The pavaex apparatus was used. The treatments were centralized in the physical therapy department of the New York Hospital.

Of 36 arteriosclerosis obliterans patients, 29, or 80.5 per cent, were improved. Three patients who experienced pain while under treatment did badly and came to amputation, probably because of a diffuse sclerosis involving the arterioles as well as major arteries.

Ten cases of acute vascular occlusion (embolism, thrombosis) were treated, with encouraging results in 9. Of 4 cases of thromboangiitis obliterans, the treatment was a failure in 3, of doubtful value in one. In no case of the whole series was there conclusive evidence that the procedure had itself caused serious complications.

L. H. H.

**Machella, T. E.:** The Velocity of Blood Flow in Arteries in Animals. *Am. J. Physiol.* 115: 632, 1936.

The velocity of blood flow in arteries may be measured by the insertion in the artery of a short length of nickel wire. If this be connected to a Kelvin-Thompson bridge and be used according to the hot-wire principle developed by Hill, the velocity of blood flow may be measured by variations in resistance. Owing to the small mass of the wire used and the intimate contact with the moving stream, the system is able to follow accurately rapid changes in velocity. The method measures velocity of flow rather than volume flow, though the latter can be estimated if the diameter of the vessel is known. The velocity curves of the carotid and femoral arteries are shown to resemble the pressure curves in these arteries and to differ from one another just as do the pressure curves.

When an animal is in good condition, the systolic velocities observed in the carotid and femoral arteries under dial-morphine anesthesia are usually 50 cm. per second or more. The mean velocities are about 9 cm. per second. Studies of the

velocity in the aorta 2 cm. distant from the aortic valves show that the flow at this point does not decrease to zero during diastole; the reservoir action of the aorta and of the aortic valves proximal to this point must, therefore, be considerable. Study of the velocity changes in the coronary arteries demonstrates that the main flow occurs during systole.

E. A.

Kaplan, T.: Frost-Bite. *Am. J. Surg.* 32: 318, 1936.

The pathology of this condition may be due to (1) change in the colloid structure of protoplasm incident to the greatly lowered temperature; (2) vasoconstriction and spasm; (3) reactionary hyperemia and transudation of serum further cutting off blood supply; and (4) rarely, thrombosis.

The clinical manifestations and therapy of frostbite are considered briefly, with several references to the literature, but with no personal findings or results included.

L. H. H.

Koch, Julius: Is the Blood Pressure Regulation on Changing Body Posture Dependent Solely on the Four Known Blood Pressure Nerve Regulators? *Ztschr. f. Biol.* 96: 314, 1935.

Denervation of the sensory regions of the root of the aorta and of the carotid sinuses has little effect on the ability of the rabbit to maintain the blood pressure when body posture is changed. The author concludes that there must be receptors in other regions than these which are capable of maintaining the blood pressure under these circumstances.

L. N. K.

Levin, E.: Circulators Quotient in Cardiac Insufficiency. *Rev. argent. de cardiol.* 2: 354, 1935.

From the assumption that minute volume of blood and circulatory quotient  $\frac{\text{Volemia} \times 60}{\text{Chronemia}}$  change always in the same general sense, the circulatory quotient was determined in twenty-seven cardiac patients, both during decompensation and recompensation, in order to seek the corresponding variations of the minute volume of blood.

The results were irregular. In 16 cases the circulatory quotient was lower during cardiac insufficiency; in 4 cases it showed no appreciable change; and in 7 cases it was higher during decompensation than after recompensation. These findings essentially agree with those of some other investigators.

The view is advanced that the minute volume of blood in cardiac patients depends on the oxygen consumed, the degree of its utilization and the reserve power of the heart. These three factors may act in the same or in different ways. Its value, if taken by itself, gives no information regarding tissue oxygenation. An apparently high minute volume of blood may be insufficient and vice versa.

AUTHOR.



## Book Reviews

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SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By George R. Herrmann, M.D., St. Louis, 1936, The C. V. Mosby Company.

The author refers to this small volume as a handbook and modestly states that it is "an attempt to provide an acceptable indexed epitome of the principles and modern conceptions of cardiologic practice." Actually, its 328 pages contain practically all the useful information found in most larger texts, presented in detail, that is ample for practitioners and students, for whom it is primarily designed. The earlier chapters deal with definitions, criteria, the details of history taking, a discussion of the instruments used in the clinical study of patients, and of the value and limitations of the x-ray and electrocardiograph. These subjects occupy less than a third of the book; the remainder is devoted to a discussion of classification of cardiac diseases, arrhythmias, the diagnosis and treatment of congestive and anginal heart failure, coronary thrombosis, bacterial endocarditis, rheumatic and syphilitic disease, the various types of chronic valvular disease, congenital lesions, and pericarditis. The final chapter is upon diseases of the peripheral vascular system.

The author's standing as a teacher and investigator and his many contributions to our knowledge of cardiovascular disease would be sufficient to guarantee the accuracy of his statements and the soundness of his views. He has, however, clearly indicated in the preface that the book is not a presentation of original work or ideas; it is, rather, a comprehensive survey of the entire field by a competent authority who has lucidly summarized our present knowledge of the subject. There are nearly a hundred illustrations, all of them clear and helpful, and many of them notable for originality. The text is written simply and with admirable clarity. There are doubtless some who will criticize the number of pages devoted to a discussion of valve lesions, but the author is too deeply in sympathy with the modern view of myocardial function to discuss these lesions from the viewpoint of twenty years ago, and his discussion is probably a sane corrective to the extreme views of those who regard valve lesions as wholly unimportant.

It is a pleasure to commend this small book to all practitioners and students who wish a brief, timely, up to date, and authoritative discussion of this field of medicine. It is far superior to any similar volume ever encountered by the present reviewer.

H. M. M.

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LE SYNDROME ENDOCRINO-HEPATO-MYOCARDIQUE: SUR UN ASPECT DES CIRRHOSSES PIGMENTAIRES. By Etienne Royer de Véricourt, Paris, 1936, Masson et Cie.

This monograph of 140 pages is devoted to a presentation of certain aspects of hemochromatosis which, the author believes, constitutes a new syndrome. This consists of multiple endocrine aplasias, hepatic cirrhosis, diffuse visceral hemosiderosis, and severe myocardial failure of a special type.

L. A. C.

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## Original Communications

### THE USE OF ETIOLOGICAL NOMENCLATURE OF HEART DISEASE IN HOSPITALS IN THE UNITED STATES\*

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NEARLY twenty-five years have elapsed since Cabot<sup>1</sup> focused attention on an etiological basis for classifying heart disease. During this time many refinements have been made in diagnosing, and additional factors have been discovered. Much of the credit for the improvement in diagnosing heart disease is due the Committee on Cardiac Clinics of the Association for the Prevention and Relief of Heart Disease in New York City, which in 1923 prepared a nomenclature covering diseases of the heart and blood vessels which it introduced into its various clinics. This nomenclature has been revised from time to time by the Heart Committee of the New York Tuberculosis and Health Association and has been adopted by the American Heart Association which now sponsors its use.<sup>2</sup> It is generally recognized that the prevention of heart disease or postponement of its more serious consequences demands that each etiological factor be attacked separately. The struggle against heart disease is essentially a war of attrition rather than a broad frontal attack.

While gathering information about the prevalence of rheumatic heart disease, rheumatic fever, and chorea among in-patient admissions to hospitals throughout the United States, this office inquired about the use of etiological nomenclature of heart disease in general. Questionnaires were sent to general hospitals and children's hospitals, most of which have capacities of 100 beds or more. While inquiries were directed at most of the hospitals approved for internships by the American Medical Association, the study was not confined to these institutions. To have done so would have excluded most of the pediatric hos-

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TABLE I

Distribution by States of Hospitals Using Etiological Nomenclature of Heart Disease for Diagnosing In-Patient Admissions During 1934. Order Based on Percentages of Hospitals Indicating Use of Etiological Nomenclature Among Entire Group Sent Questionnaire

STANDING	STATE	NUMBER OF HOSPITALS SENT QUESTIONNAIRE	NUMBER OF HOSPITALS ANSWERING QUESTION ABOUT CLASSIFICATION	NUMBER OF HOSPITALS USING ETIOLOGICAL NOMENCLATURE	PER CENT OF TOTAL NUM- BER USING ETIOLOGICAL NOMENCLATURE	PER CENT OF HOSPITALS ANSWERING QUESTION USING ETIOLOGICAL NOMENCLATURE
1	Maine	12	10	7	58.3	70.0
2	Connecticut	19	18	11	57.9	61.1
3	Dist. of Columbia	9	7	5	55.6	71.4
4	Rhode Island	11	8	6	54.6	75.0
5	New Jersey	47	37	23	48.9	62.2
6	New York	123	90	60	48.8	66.7
7	Massachusetts	64	46	30	46.9	65.2
8	Missouri	44	33	20	45.5	60.6
9	Pennsylvania	129	101	57	44.2	56.4
10	Florida	14	11	6	42.9	54.6
11	Louisiana	14	8	6	42.9	75.0
12	Colorado	13	10	5	38.5	50.0
13	Tennessee	26	18	10	38.5	55.6
14	Kansas	21	13	8	38.1	61.5
15	California	64	49	24	37.5	49.0
16	North Dakota	11	6	4	36.4	66.7
17	Nebraska	17	11	6	35.3	54.5
18	Maryland	21	12	7	33.3	58.3
19	New Mexico	9	5	3	33.3	60.0
20	Iowa	31	16	10	32.3	62.5
21	Ohio	61	43	19	31.2	44.2
22	Texas	78	52	24	30.8	46.2
23	Alabama	10	7	3	30.0	42.9
24	Oregon	21	11	6	28.6	54.6
25	Indiana	33	21	9	27.3	42.9
26	Michigan	48	30	13	27.1	43.3
27	Georgia	19	9	5	26.3	55.6
28	Illinois	65	40	17	26.2	42.5
29	Washington	31	20	8	25.8	40.0
30	Minnesota	35	25	9	25.7	36.0
31	Delaware	4	2	1	25.0	50.0
32	South Dakota	16	11	4	25.0	36.4
33	West Virginia	35	16	8	22.9	50.0
34	Wisconsin	49	24	11	22.5	45.8
35	Idaho	9	5	2	22.2	40.0
36	Mississippi	24	12	5	20.8	41.7
37	Kentucky	17	10	3	17.7	30.0
38	South Carolina	18	9	3	16.7	33.3
39	North Carolina	37	21	6	16.2	28.6
40	Virginia	37	23	6	16.2	26.1
41	Vermont	13	9	2	15.4	22.2
42	New Hampshire	15	7	2	13.3	28.6
43	Nevada	9	5	1	11.1	20.0
44	Utah	10	6	1	10.0	16.7
45	Wyoming	10	4	1	10.0	25.0
46	Oklahoma	24	11	2	8.3	18.2
47	Montana	18	8	1	5.6	12.5
48	Arizona	6	2	0	0	0
49	Arkansas	10	1	0	0	0
Totals		1,461	953	480	32.9	50.4

pitals and many private hospitals with unquestionably high standards but not meeting all of the requirements for recognition. Furthermore, in quite a few states not many hospitals are approved for internships. Hospitals belonging to the federal government, with the exception of a few Indian hospitals, were excluded as their beneficiaries are limited to certain select groups among whom there are but few children.

Inquiries were sent to 1,461 hospitals, of which 953 answered the question about the use of an etiological nomenclature during the year 1934. Others stated that they had adopted etiological classifications in 1935. These, however, were not included in the present study. Four hundred eighty-one indicated the use of an etiological terminology. This comprised 32.9 per cent of all the hospitals to which questionnaires were sent, or 50.4 per cent of those replying. These hospitals have either adopted systems of nomenclature embodying an etiological classification of heart disease or have incorporated an etiological nomenclature, usually that of the American Heart Association, into existing systems.

In Table I is shown the distribution by states and the District of Columbia of hospitals using etiological nomenclature. On the basis of the percentage indicating the use of etiological terminology in the entire series, hospitals in Maine, Connecticut, the District of Columbia, Rhode Island, New Jersey, New York, Massachusetts, Missouri, Pennsylvania, Florida, Louisiana, and Colorado employed it most frequently and in the order mentioned. Eight of these twelve areas are located along the northeastern seaboard. On the other hand, etiological nomenclature does not appear to be so popular in most of the western states. If this table is studied from the basis of the number of hospitals answering the inquiry the percentages are somewhat higher, and the results, although in some cases slightly different, are essentially similar.

The extent to which etiological nomenclature is used in various sections of the United States is shown in Table II. Etiological systems of classification are employed more frequently by hospitals in the Middle Atlantic and New England states than by hospitals in other parts of the country and are used to a lesser extent in the Rocky Mountain states than in other sections. It is noteworthy that use of etiological nomenclature is more in vogue in that part of the country where the American Heart Association is strongest. Its popularity in New England is largely attributable to the New England Heart Association.

In Table III a study is made of the use of etiological nomenclature among hospitals approved for internships by the American Medical Association. Of 572 hospitals to which inquiries were sent, replies to this question were received from 474. Two hundred eighty-eight hospitals, 50.3 per cent of the total number from which information was sought, or 60.8 per cent of the hospitals replying to this question, indicated the use of etiological terminology. While it cannot be postulated that hospitals approved for internships necessarily have higher stand-

TABLE II

DISTRIBUTION BY SECTIONS OF THE UNITED STATES OF HOSPITALS USING ETIOLOGICAL NOMENCLATURE OF HEART DISEASE

SECTION	NUMBER OF HOSPITALS SENT QUESTIONNAIRE	NUMBER OF HOSPITALS REPLYING TO QUESTION REGARDING NOMENCLATURE	NUMBER OF HOSPITALS USING ETIOLOGICAL NOMENCLATURE	PER CENT OF NUMBER SENT QUESTIONNAIRE	PER CENT OF NUMBER REPLYING TO QUESTION ABOUT NOMENCLATURE
New England (Me., N. H., Vt., Mass., R. I., Conn.)	134	98	58	43.3	59.2
Middle Atlantic (N. Y., N. J., Pa.)	299	228	140	46.8	61.4
East North Central (Ohio, Ind., Ill., Mich., Wis.)	256	158	69	27.0	43.7
West North Central (Minn., Iowa, Mo., N. D., S. D., Neb., Kan.)	175	115	61	34.9	53.0
South Atlantic (Del., Md., D. C., Va., W. Va., N. C., S. C., Ga., Fla.)	194	110	47	24.2	42.7
East South Central (Ky., Tenn., Ala., Miss.)	77	47	21	27.3	44.7
West South Central (Ark., La., Okla., Tex.)	126	72	32	25.4	44.4
Mountain (Mont., Idaho, Wyo., Colo., N. M., Ariz., Utah, Nev.)	84	45	14	16.7	31.1
Pacific (Wash., Ore., Calif.)	116	80	38	32.8	47.5
Totals	1,461	953	480	32.9	50.4

ards than other institutions, these hospitals have met certain standards regarding size, organization, and equipment. In them young physicians receive much of their practical clinical training. Many practitioners, especially those settling in the smaller towns and rural areas, continue to diagnose in terms taught them in medical school and hospital days. Hence it is desirable that such hospitals employ the best terminology available.

Although there are notable exceptions a larger proportion of hospitals in the New England and Middle Atlantic states have adopted etiological classifications than in other parts of the country. This becomes espe-

TABLE III

DISTRIBUTION BY STATES OF HOSPITALS APPROVED FOR INTERNESHIPS BY THE  
AMERICAN MEDICAL ASSOCIATION USING ETIOLOGICAL NOMENCLATURE  
OF HEART DISEASE

STANDING	STATE	NUMBER HOSPITALS SENT QUESTIONNAIRE	NUMBER HOSPITALS ANSWERING QUESTION ABOUT CLASSIFICATION	NUMBER REPORTING USE OF ETIOLOGICAL NOMENCLATURE	PER CENT OF HOSPITALS SENT QUESTIONNAIRE	PER CENT OF HOSPITALS ANSWERING QUESTION ABOUT CLASSIFICATION
1	Maine	4	4	4	100.0	100.0
2	New Hampshire	1	1	1	100.0	100.0
3	Rhode Island	4	4	4	100.0	100.0
4	West Virginia	4	3	3	75.0	100.0
5	Missouri	22	19	15	68.2	78.9
6	Florida	3	3	2	66.7	66.7
7	New York	78	65	50	64.1	76.9
8	Connecticut	16	15	10	62.5	66.7
9	New Jersey	30	25	18	60.0	72.0
10	Tennessee	10	9	6	60.0	66.7
11	Pennsylvania	69	62	41	59.4	66.1
12	Massachusetts	31	28	17	54.8	60.7
13	Delaware	2	1	1	50.0	100.0
14	District of Columbia	8	7	4	50.0	57.1
15	Georgia	6	4	3	50.0	75.0
16	Kansas	6	6	3	50.0	50.0
17	Louisiana	4	3	2	50.0	66.7
18	North Dakota	2	1	1	50.0	100.0
19	Oregon	4	4	2	50.0	50.0
20	South Carolina	4	3	2	50.0	66.7
21	Texas	18	15	9	50.0	60.0
22	Vermont	2	1	1	50.0	100.0
23	California	25	25	12	48.0	48.0
24	Maryland	13	11	6	46.2	54.5
25	Colorado	9	7	4	44.4	57.1
26	Indiana	12	9	5	41.7	55.6
27	Washington	12	11	5	41.7	45.5
28	Illinois	29	26	12	41.4	46.2
29	Iowa	10	6	4	40.0	66.7
30	Nebraska	10	6	4	40.0	66.7
31	Michigan	21	16	8	38.1	50.0
32	Ohio	27	18	10	37.0	55.6
33	Wisconsin	22	14	8	36.4	57.1
34	Minnesota	13	11	4	30.8	36.4
35	Virginia	7	7	2	28.6	28.6
36	North Carolina	8	7	2	25.0	28.6
37	Utah	5	4	1	20.0	25.0
38	Kentucky	6	6	1	16.7	16.7
39	Oklahoma	6	3	1	16.7	33.3
40	Alabama	3	2	0	0	0
41	Arkansas	4	1	0	0	0
42	Montana	2	1	0	0	0
Totals		572	474	288	50.3	60.8

cially manifest if only the states with a considerable number of hospitals reporting are taken under consideration. Missouri, a midwestern state, on the other hand, heads the list of states with a large number of hospitals reporting.

In Table IV the use of etiological nomenclature in teaching hospitals is shown. These include hospitals directly under the control of medical

TABLE IV

DISTRIBUTION BY STATES OF TEACHING HOSPITALS USING ETIOLOGICAL NOMENCLATURE OF HEART DISEASE

STANDING	STATE	NUMBER HOSPITALS SENT QUESTIONNAIRE	NUMBER HOSPITALS ANSWERING QUESTION ABOUT CLASSIFICATION	REPORTING USE OF ETIOLOGICAL NOMENCLATURE		
				NUMBER	PER CENT OF HOSPITALS SENT QUESTIONNAIRE	PER CENT OF HOSPITALS ANSWERING QUESTION ABOUT CLASSIFICATION
1	Connecticut	1	1	1	100.0	100.0
2	Indiana	3	3	3	100.0	100.0
3	Kansas	2	2	2	100.0	100.0
4	Louisiana	2	2	2	100.0	100.0
5	Massachusetts	8	8	8	100.0	100.0
6	North Carolina	1	1	1	100.0	100.0
7	Oklahoma	1	1	1	100.0	100.0
8	South Carolina	1	1	1	100.0	100.0
9	New York	24	23	22	91.7	95.7
10	Georgia	4	3	3	75.0	100.0
11	Maryland	4	3	3	75.0	100.0
12	Pennsylvania	17	16	12	70.6	75.0
13	Missouri	10	9	7	70.0	77.8
14	California	6	6	4	66.7	66.7
15	Illinois	12	12	8	66.7	66.7
16	Nebraska	5	3	3	60.0	100.0
17	Wisconsin	5	4	3	60.0	75.0
18	Ohio	11	7	6	54.5	85.7
19	Colorado	2	2	1	50.0	50.0
20	Oregon	4	4	2	50.0	50.0
21	Tennessee	4	4	2	50.0	50.0
22	Texas	4	4	2	50.0	50.0
23	Virginia	2	2	1	50.0	50.0
24	District of Columbia	7	6	3	42.9	50.0
25	Michigan	3	2	1	33.3	50.0
26	Minnesota	4	3	1	25.0	33.3
27	Iowa	1	1	0	0	0
28	Kentucky	1	1	0	0	0
Totals		149	134	103	69.1	76.9

schools and affiliated institutions whose clinical facilities are available for teaching purposes. Practically all of the teaching hospitals, with the exception of certain children's hospitals, are on the list approved for internships. Inquiries were sent to 149 teaching hospitals. Replies were received from 134 hospitals, 103 of which indicated the use of

such a classification. This comprised 69.1 per cent of the total, or 76.9 per cent of those replying. All of the nineteen pediatric teaching hospitals replied to the inquiry. Fourteen, or 73.7 per cent, indicated the use of an etiological nomenclature.

In eight of twenty-eight states (including the District of Columbia) every teaching hospital of which inquiries were made stated that it used some form of etiological nomenclature. On the basis of hospitals answering the questionnaire, all of the teaching hospitals in eleven states indicated the use of etiological nomenclature.

From the above it is evident that the most of the more progressive hospitals, especially those engaging in clinical research and used for teaching purposes are employing etiological terms in diagnosing and recording cases of heart disease. It is difficult to see how it is possible to do otherwise and yet interpret clinical findings in the language of modern literature dealing with heart disease.

There appears to be but slight relationship between the type of ownership or control of hospitals and the use of etiological nomenclature of heart disease. State, municipal (including county), incorporated, non-profit association, church and fraternal hospitals, and those owned by private individuals employ etiological nomenclature to about the same extent, the differences being determined by the section of the country and whether used for teaching or research purposes rather than by any factors inherent in the type of control. This does not apply to smaller hospitals not included in this series. Most of these are mainly surgical hospitals, having relatively few medical cases. The records in such cases often leave much to be desired. Another exception not included in this series are the hospitals of the federal government. With the exception of a few isolated instances, none have adopted etiological classifications. In many government hospitals, notably those of the Veterans Administration,<sup>3</sup> the use of the etiological nomenclature of the American Heart Association is encouraged but is not the basis for official records. The United States Public Health Service employs an etiological nomenclature in its research activities.

The relationship between the use of etiological nomenclature and the size of a city is difficult to determine. In general, its use is more common in the larger cities. Although there are exceptions, etiological nomenclature is more in vogue in the smaller cities which are satellites of the larger medical centers or are the location of state universities with schools of medicine. In others its use is not so frequent as in the larger cities. In the hospitals in smaller towns the use of etiological nomenclature is definitely less common.

#### SUMMARY AND CONCLUSIONS

1. Four hundred eighty, or 32.9 per cent, of 1,461 general and children's hospitals to which inquiries were made indicated the use of



etiological nomenclature in diagnosing heart disease among in-patient admissions. Of 953 hospitals replying to the question about etiological nomenclature, 50.4 per cent stated that they used it.

2. Among 572 hospitals approved for internships by the American Medical Association, 288, or 50.3 per cent, of the total number, or 60.8 per cent of the 474 hospitals from which replies were received, indicated the use of etiological nomenclature.

3. Among 149 teaching hospitals, 103, or 69.1 per cent of the total, or 76.9 per cent of the 134 from which answers were received, indicated the use of etiological terminology.

4. It is evident from the above that most of the more progressive institutions have adopted etiological classifications.

5. The extent to which etiological nomenclature of heart disease is used varies considerably in different sections of the country and among the several states. In general, it is more in use in New England and in the Middle Atlantic states than in other parts of the country. It is used to a greater extent in the larger cities and in their vicinity than in the more isolated and smaller communities.

The author is indebted to Dr. Charles C. Wolferth, of the Robinette Foundation of the University of Pennsylvania for a number of helpful suggestions in the preparation of this paper.

#### REFERENCES

1. Cabot, R. C.: The Four Common Types of Heart Disease, *J. A. M. A.* 63: 1461, 1914.
2. Criteria for Classification and Diagnosis of Heart Disease, ed. 3, New York Tuberculosis and Health Association, 1932.
3. Matz, Philip B.: Chief, Research Subdivision, U. S. Veterans Administration (personal communication to the author).

## A SURVEY OF HEART DISEASE MORBIDITY IN SAN FRANCISCO\*†

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THE report herein presented is unique in that a municipal Department of Public Health recognized the importance of a survey of heart disease morbidity and assembled its facilities for the collection of the main mass of these data. Reports of heart disease morbidity are open to criticism on the grounds that case distribution even in the same geographical locality is heavily influenced by many variable elements. Some of the most important influences we may enumerate as follows: the time of year of the report; the diagnostic ability of the physicians reporting and their adherence to certain standards of classification; the social status of the patients; the locale of the patient when seen, i.e. office, out-patient dispensary, clinic ward, home or private hospital room, and the limitations of the physicians' practices or the case selection of special clinics or hospitals.

In all of the reports previously assembled from various geographical locations, certain of these variables have been taken into account but in no instance, including our own, have all been controlled. In presenting this survey from San Francisco, we are comparing three groups: (1) cases reported in a city-wide survey made by the San Francisco Department of Public Health‡; (2) patients reported in the single month of January, 1932, from the private office, home and hospital practices of eighteen physicians with a known high level of diagnostic ability;

\*From the Department of Public Health of the City and County of San Francisco.

†The authors wish to acknowledge the assistance of Rosemary T. Kobes, of the San Francisco Heart Committee, Hilda F. Welke, of the Division of Vital Statistics, San Francisco Department of Public Health, and of the staffs of the Out-Patient Clinics of the University of California and Mount Zion Hospitals for their active participation and for the data submitted by them for study; and to express their appreciation to the various other agencies and individuals who participated and supplied reports of cases, particularly, to the San Francisco Heart Committee for its continued interest and stimulation, as well as the active participation of its members.

‡Two surveys were conducted by the San Francisco Department of Public Health, the first for a period of three months beginning March 1, 1932, the second for one year from August 1, 1932. Blank forms were furnished by the Department in each of these surveys, to all physicians and all hospitals in the city. These forms (Table I) were for the purpose of recording certain facts in the case histories of heart disease patients and were to be returned to the Department of Public Health at regular intervals in postage-free envelopes. About 58 physicians reported immediately that they did not see heart cases and consequently could make no returns. During the first survey, 108 physicians and 8 hospitals made reports; in the second survey, 133 physicians and 14 hospitals reported, with the result that about 3,300 cases were made available for study. A preliminary review of these cases, however, disclosed many in which essential information was lacking, and therefore it became necessary to discard them. Some duplications, also, were found, but a total of 3,141 cases remained upon which analyses and compilations were made. In 1933, there were in San Francisco 1,682 registered physicians, and the estimated population for the city for the same year was 681,325.

and (3) from the cardiac out-patient clinics of the University of California and Mount Zion Hospitals, combined, in the same month of January, 1932.

It is believed that certain consistent occurrences may be discovered for the community by agreement in these groups.

TABLE I

DEPARTMENT OF PUBLIC HEALTH  
City and County of San Francisco

HEART DISEASE MORBIDITY STUDY

Patient's Initials..... Case Number.....  
(Use this number in your records.)  
Age..... Sex..... Race..... Marital Status: S\_\_\_\_ M\_\_\_\_ W\_\_\_\_ D\_\_\_\_  
Occupation..... Resident?..... Nonresident?.....  
Patient previously treated for heart disease?..... If so, when?.....  
Heart disease in other members of family?.....  
Chief Complaint.....  
Rheumatic Fever Syndrome: Acute Rheumatic Fever..... Choreia.....  
"Growing Pains"..... Other (be specific).....  
Duration of Heart Disease..... Duration of Etiological Factors.....

*Diagnosis:*

1. Etiological: Coronary Arteriosclerosis or Degeneration..... Hyperten-  
sion..... Rheumatic Fever..... Syphilis..... Congenital.....  
Thyroid..... Functional..... Subacute Bacterial Endocarditis.....  
Other Causes (specify).....
2. Anatomical: Myocarditis: Infectious..... Degenerative.....  
Pericarditis: Acute..... With effusion..... Adhesive.....  
Valves: Aortic Mitral Tricuspid Pulmonary  
Insufficiency..... Insufficiency..... Insufficiency..... Insufficiency.....  
Organic..... Organic.....  
Relative..... Relative.....  
Stenosis..... Stenosis..... Stenosis..... Stenosis.....  
Acute Coronary Occlusion..... Involvement of great vessels and/or  
other heart lesions: (specify).....
3. Physiological: Congestive Failure (With dyspnea, edema, etc.).....  
Angina Pectoris..... Arrhythmias (specify type).....

*Functional Capacity:*

1. Ordinary physical ability..... 2. Slight limitation.....
3. Marked limitation..... 4. Complete physical disability.....

Cardiogram.....

Date.....

Use check (✓) where possible.

.....M.D.  
.....Address

Certain local conditions exist in San Francisco which might influence heart disease. The climate is moist but remarkably equable. For the ten-year period, 1920-1930, the average January temperature was 49.2° F.; the average July temperature was 59.9° F. In 1934 the average relative humidity, in per cent, for January was 76, for July, 80, with an average for the year of 76. For comparison it may be of interest to point out that in New York the mean temperature for January, in 1934, was

30.9° F., for July, 74.8° F.; the relative humidity, in per cent, for January was 73, for July, 75, with an annual average of 74. (The readings for humidity are those taken shortly after sunrise. In both cities there is a variation in the readings throughout the day.)

It is commonly believed that typical acute rheumatic fever is much lower in its incidence in San Francisco than in cities of the Middle West or on the Atlantic seaboard, of nearly equal latitude; as, for example, New York (40 degrees 48 minutes), Philadelphia (39 degrees 58 minutes), Saint Louis (38 degrees 38 minutes), as compared with San Francisco (37 degrees 47 minutes). It should be pointed out also, perhaps, that the rarity of the occurrence of the rheumatic syndrome in tropical and subtropical regions is well recognized.

There is a relatively higher percentage of Orientals and a lower percentage of negro population in San Francisco. For the year, 1930, the negro population of San Francisco, was only 0.5 per cent of the total population, while the Chinese constituted 3 per cent. In New York, on the other hand, the negro population was 4.7 per cent of the total population, and all other colored racial groups, including Chinese, were but 0.2 per cent.

There is in the San Francisco population group a somewhat greater percentage of elderly individuals, made up, in part at least, of those who migrate to California after retirement from more active lives elsewhere. Table II shows the age composition of the population.

TABLE II

1930	PER CENT UNDER 15 YR.	PER CENT 15-44 YR.	PER CENT 45 YR. AND OVER
New York	24.4	54.5	21.1
San Francisco	17.0	55.0	28.0
Los Angeles	20.0	60.0	20.0
Pasadena (1934)	Under 45 yr., 61.2%		Over 45 yr., 38.8%

Likewise, no inconsiderable number of individuals in ill health tend to migrate to warmer climates, and we may therefore find a large group of recurrent acute rheumatic fever patients here whose cardiac lesions have developed prior to the establishment of residence in this community. Of interest, also may be the fact that the region is recognized as one in which the incidence of endemic simple goiter and Graves' disease is higher than average throughout the United States.

In a letter to all licensed medical practitioners of San Francisco on March 15, 1932, the Director of Public Health of San Francisco informed them that from that date and for a period of three months, by regulation of the Department of Public Health, heart disease and acute rheumatic fever were made reportable. On August 1, 1932, this regulation was extended for the period of one year. At this time an explanatory letter and a supply of revised forms were sent to all registered physicians and hospitals, enlisting their cooperation in the survey.

The revised form is shown in Table I. The data which we hoped to obtain from these forms are apparent. Certain checks on the diagnoses are permitted by the data given, as, for example, the electrocardiogram findings. Uncomplicated hypertension was entered as distinct from arteriosclerosis, uncomplicated and with hypertension, and the functional capacity was defined rather than offering the American Heart Association's classification of 1, 2a, 2b, and 3, without explanation.

The material from these sources was assembled separately as (1) the preliminary survey of March 15, 1932, to June 15, 1932, and (2) the final survey of August 1, 1932, to August 1, 1933. All the data were used in compiling Table III and column (c) of Table IV, but because of certain changes in the forms used beginning August 1, 1932, with certain indicated exceptions, only the second survey of 2,270 cases was used for Tables V, VI, VII and VIII.

An attempt was made, in analyzing the returned forms, to determine whether the agent responsible for the cardiac incapacity was (1) unquestionably the primary cause, (2) a doubtful agent, or (3) definitely a secondary or complicating cause to another primary cardiac disease. Only five of the etiological groups are included in these assembled data as shown in Table III.

TABLE III

	FRANK FACTOR (%)	QUESTIONABLE FACTOR (%)	SECONDARY FACTOR (%)
Congenital	88.8	3.6	7.6
Rheumatic fever	74.6	11.8	13.6
Syphilis	59.7	6.8	33.5
Thyroid	54.3	14.1	31.6
Arteriosclerosis	57.0	6.2	36.8

Arteriosclerosis, syphilis and thyroid disease are shown to be frequently complicating diseases. This is of special interest in thyrotoxicosis in which opinion is generally in agreement that damage from that source is rarely permanent unless superimposed on underlying cardiac damage.

Consideration of Table IV reveals that there is a remarkable agreement in certain etiological groups between the well-controlled surveys in columns (a) and (b), and the definitely uncontrolled survey of physicians and clinics of unknown diagnostic capacities in column (c). This leads one to the impression that the entire survey probably represents a fairly reliable index of the proportionate incidence of the various types of heart disease in San Francisco.

The two clearest discrepancies in these three groups are: in syphilitic heart disease, which, as expected, is found to be less frequent in the higher social group under the care of private physicians than in the clinic group; and in thyroid heart disease which is probably less well

TABLE IV  
 CLASSIFICATION OF CASES—PER CENT IN EACH GROUP

CLASSIFIED GROUPS	(A)		(B)		TOTAL (A) AND (B)		(C)		TOTAL (A), (B) AND (C)
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	
Congenital	11	4.0	8	5.9	19	4.8	179	5.5	198
Rheumatic fever	58	21.0	28	20.6	86	21.8	702	22.3	788
Syphilis	5	1.8	22	16.1	27	6.9	226	7.2	233
Thyroid	20	7.3	4	2.9	24	6.1	77	2.5	101
Subacute bacterial endocarditis	2	0.7			2	0.5	31	0.99	33
Arteriosclerosis (uncomplicated)	70	25.4	10	7.3	80	20.3	734	23.4	814
Arteriosclerosis and hypertension	30	11.0	23	16.9	53	13.4	529	16.9	582
Hypertension (uncomplicated)	22	8.0	25	18.3	47	11.9	195	6.2	242
Total—Art.-Hyper. above	122	44.4	58	42.5	180	45.7	1458	46.5	1638
Cor pulmonale	3	1.1	11	8.1	14	3.2	10	0.4*	24
Functional	27	9.8	5	3.7	32	8.1	192	6.1	224
Total all cases classified†	275				394		3141		3535

\*Includes cases of second city-wide survey only.

†Includes the "miscellaneous" and "unclassified" groups.

recognized by the general practitioner than by the well-trained diagnostician. The incidence of thyrotoxicosis may vary in different social groups, but these data only suggest such a possibility.

An explanation of certain etiological classifications in Table IV is necessary. Under "rheumatic fever" are included all cases with definite histories of rheumatic fever, "growing pains" or chorea, as well as mitral stenosis of doubtful etiology. Under "thyroid" are entered those cases with definite thyrotoxicosis. Only two examples of "myxedema heart" were reported in the series, and these have been placed in the "miscellaneous" and "unclassified" groups. The cases demonstrating frank, presumably uncomplicated, hypertension have been placed in a separate and distinct category from the arteriosclerosis\* group, which includes cases in which there was evidence of elevation of blood pressure as well as uncomplicated coronary arteriosclerosis. Included in the arteriosclerosis and hypertension groups were the following percentages of those cases of acute coronary artery occlusion under active care: 17 per cent in the controlled one-month physicians' survey, 3 per cent in the one-month clinic survey, and 5.6 per cent in the second city-wide survey, with approximately 2.5 per cent incidence in each category.

In the various groups, chiefly the "miscellaneous," are included thirty-two cases of pericarditis, grouped as follows: in the one-month controlled private physician survey were seven cases of acute pericarditis and one of adhesive pericarditis; in the one-month controlled clinic survey were one acute pericarditis and two adhesive pericarditis cases; in the second city-wide survey, of 2,270 cases, were thirteen cases of acute pericarditis, two of tuberculous pericarditis and six of adhesive pericarditis. The total incidence was 1.2 per cent. Undoubtedly some of the adhesive pericarditis cases are of unrecognized tuberculous origin.

Scarlet fever was credited as the etiological factor in eleven cases, giving an incidence of 0.41 per cent, in 2,664 cases representing all but the first city-wide survey. Diphtheria was given as a cause in seven cases, an incidence of 0.26 per cent, in this same total number of cases.

Cases of emphysema with evidences of pulmonary arteriosclerosis formed a large portion of the group of cor pulmonale. The high incidence in the one-month clinic survey is due to the special study of an assembled group of patients presenting this type of heart disease, in both the University of California and Mount Zion clinics.

Other causes of cardiac damage, such as trauma, rarer infections, intoxication and neoplasms, are included in the miscellaneous group. The "functional" classification includes effort syndrome and arrhythmias without other evidence of cardiac disease.

In comparing the incidences of the various etiological groups with those obtained in the East, in the Middle West, in the Rocky Mountain

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\*This term is being replaced by "coronary arteriosclerosis" in classification schemes.

district, in the South, and in the Northwest,<sup>1-15</sup> certain unusual characteristics occur in this survey of San Francisco. The frequency of congenital heart lesions is much higher (5.5 per cent) than in any previous survey. This high percentile incidence has likewise occurred in a survey now under way on the morbidity of heart disease in the San Francisco children of the school and preschool groups, and is probably due to the relative infrequency of rheumatic heart disease in these children. This probably influenced the entire survey figures since one of the most faithful reporting sources of cases was the Municipal School Cardiac Diagnostic Center.

The data on congenital heart disease in Tables V, VI, and VII, show certain interesting characteristics; namely, the higher incidence in females and the predominance in the lower age groups, which fact accounts for the relatively higher percentage in this group as compared with others, of residents, of unmarried social status, and preschool and school occupations. The high percentage with normal physical capacity may mean that in some of these cases the diagnosis of congenital heart disease may have been made erroneously, a circumstance which may be another explanation of the high proportional incidence of this type of heart disease in the survey. This normal function in so many cases may also be explained by the fact that many of these, seriously handicapped because of congenital heart disease, die early in life. This likewise explains, perhaps, the distribution of cases according to duration, with many reported as under six months and again over five years, with a lower frequency in the intervening time intervals.

With the exception of Texas, Oregon, and Virginia, the reported and surveyed incidence of rheumatic heart disease in our study is definitely lower than in other American surveys. Seegal, Seegal and Jost<sup>16, 17</sup> have shown that the incidence of the acute rheumatic syndrome in various hospitals in the United States, diminishes in the lower latitudes, and many others have pointed out its relative infrequency in semitropical and tropical countries. In Table V, column 3, it is found that only 78 per cent of the rheumatic subjects were residents. From other analyses of known cases in school children, it was found that residence was established in San Francisco not infrequently because the affected individuals had acquired their rheumatism prior to coming to California, and, indeed, the family often had migrated here because of the probable beneficial effect of the milder climate of this area.

From Table V it will be seen that valvular involvement is practically universal in this group and that auricular fibrillation occurs in 13 per cent of the cases recorded. It is somewhat surprising that this table fails to show a higher incidence of heart disease in the families of patients with rheumatic involvement than in other etiological classes.

In the assembled data of Dauer<sup>18</sup> on mortality rates of heart disease in various portions of the United States, a situation is found in Cali-



TABLE V  
(2,270 CASES REPORTED IN SECOND CITY-WIDE SURVEY)

	STATISTICAL SUMMARY				ANATOMICAL FACTORS			PHYSIOLOGICAL FACTORS		
	PER CENT IN EACH GROUP*				ACUTE CORONARY ARTERIAL OCCLUSION	VALVULAR INVOLVEMENT	CONGESTIVE FAILURE	ANGINA PECTORIS	AURICULAR FIBRILLATION	A-V HEART-BLOCK
	M	F	RESIDENT	HEART DISEASE IN FAMILY						
Congenital	42	58	92	21	--	21	41	--	--	--
Rheumatic fever	49	51	78	22	--	95	28	0.3	13	1
Syphilis	83	17	78	18	2	35	44	7	3	2
Thyroid	21	79	60	14	--	42	19	2	17	1
Subacute bacterial endocarditis	71	29	90	19	--	88	36	--	18	--
Miscellaneous†	69	31	80	21	--	24	52	--	8	4
Arteriosclerosis	66	34	82	23	9	25	40	11	12	3
Hypertension	45	55	73	20	--	24	31	4	11	3
Functional	53	47	93	23	--	33	4	--	--	4
Unclassified	60	40	No analysis made in this group							
Total	59	41	81	22	7	48	35	7	9	1

\*Per cent based on total cases in each group, exclusive of those cases in which the particular item of information was not stated.

†Miscellaneous: This group includes those cases in which the etiological factors are named as Communicable Disease, Pulmonary Heart Disease, or Pericarditis.

fornia similar to that in the southern states, as compared to north-eastern and east north-central states: in the former, the mortality rates in the age group of 5 to 9 years are generally about one-third of the rates in the age group of 20 to 29 years, whereas in the latter states, the rates are approximately one-half. Thus, California from 1926 to 1929 had a heart disease mortality rate of 8.0 per 100,000 in the age group of 5 to 9, and 25.1 per 100,000 in the age group of 20 to 29, whereas Connecticut had rates of 14.9 and 26.0, respectively, in these groups. For all ages California occupies a middle position, with a mortality rate of 240 as compared to the highest rate of 291 for New Hampshire and 110 in Tennessee, Mississippi, and Wyoming. As previously stated, in a survey now in preparation by some of us on morbidity in San Francisco school children, there is an apparent striking increase in the incidence of rheumatic heart disease above the age of thirteen years, although the commonest age of onset, as reported by Coombs and others, is seven years.

That the disease takes insidious forms in San Francisco, as well as certain southern localities, seems probable, even though the percentage of rheumatic heart disease incidence, as one among all types of heart disease reported in this survey, namely 22.2, is not strikingly lower than that found in surveys in the Northeast and Middle West. In our study the striking difference between clinic and private patient groups noted

in many of the other surveys was not found, namely 20.6 per cent in clinic services and 21.0 per cent in private cases. This may be due to the better living conditions in poorer homes as found in this city, compared with the conditions found in the more congested larger eastern cities. No comparable study of mortality in rheumatic heart disease has been made in San Francisco, but if the relation between the morbidity survey in Virginia, which showed 22 per cent incidence, and the mortality survey by Hedley<sup>19, 20</sup> in adjacent Washington, D. C., which showed 13.3 per cent, obtains in San Francisco, then San Francisco probably has a mortality rate of this same magnitude, since our reported morbidity of 22.2 per cent is almost identical with that for Richmond.

A study of Table VI shows that rheumatic heart disease has no unusual incidence in negro or Oriental races; that, of their youth a high

TABLE VI  
STATISTICAL SUMMARY  
(2,270 CASES REPORTED IN SECOND CITY-WIDE SURVEY)

GROUPS	PER CENT OF ALL POP. (%)	CONGENITAL (%)	RHEUMATIC FEVER (%)	SYPHILIS (%)	THYROID (%)	SUBACUTE BACT. ENDOCARDITIS (%)	MISCELLANEOUS (%)	ARTERIO- SCLEROSIS (%)	HYPERTENSION (%)	FUNCTIONAL (%)	TOTAL
Total cases analyzed		134	473	179	57	21	45	925	163	184	2,181†
<i>Color—Race</i>											
White	93.8	97.8	97.3	93.7	100.0	95.2	100.0	97.8	93.9	97.9	97.3
Negro	0.6	---	0.6	4.0	---	4.8	---	1.7	4.3	---	1.5
Chinese	2.6	2.2	1.7	2.3	---	---	---	0.4	0.6	1.6	1.0
Japanese	1.0	---	0.4	---	---	---	---	0.1	0.6	0.5	0.2
Other	2.0	---	---	---	---	---	---	---	0.6	---	---
Not stated	---	---	---	1.1	0.8	---	---	0.7	---	---	0.4
<i>Marital Status</i>											
Single	46.0	88.8	50.2	34.2	16.5	42.8	34.1	21.3	16.0	90.7	38.8
Married	43.0	9.0	38.0	38.8	56.3	47.6	54.6	43.2	55.8	7.7	38.0
Widowed	6.9	1.5	8.6	18.0	21.8	---	6.8	29.8	21.2	---	18.2
Divorced	3.1	0.7	3.2	9.0	5.4	9.6	4.5	5.7	7.0	1.6	5.0
Not stated	1.0	---	1.5	0.6	1.6	---	2.2	3.2	4.2	1.1	2.4
<i>Occupation</i>											
Preschool		28.7	2.5	---	---	---	---	---	---	2.8	2.8
School		59.7	27.5	---	---	15.0	11.9	---	0.7	86.1	17.9
Domestic		8.5	31.7	23.9	64.0	20.0	28.6	29.7	49.3	7.0	28.4
Sedentary		---	17.9	25.1	22.0	25.0	16.7	27.6	26.8	1.8	20.7
Requiring physical labor		3.1	20.4	51.0	14.0	40.0	42.8	42.7	23.2	2.3	30.2
Not stated		3.7	5.7	8.9	12.3	4.8	6.7	10.8	15.3	7.1	9.0

\*Percentages are based only on those cases reporting the data indicated in the group. The "not stated" percentage is based on the total number of cases reported. This likewise applies to Tables VII and VIII.

†This total does not include 89 cases not classified because of insufficient information. Total cases reported are 2,270.

percentage are unmarried; and that relatively few (20.4 per cent) are in occupations requiring physical labor. The functional capacity of those presenting evidence of rheumatic heart disease is almost equally distributed through the four grades (Table VII). The duration of the disease in the higher age groups of over ten years is somewhat greater than that generally noted. The age distribution (Table VIII) at the time of reporting is about as expected, with 58.3 per cent of the cases between the ages of ten and forty years, with a rapid increase in number up to the age of ten and a slow decrease after the age of forty.

Syphilitic heart disease is about as common as found in other surveys, except in those cities in which the population includes a large negro group. As seen in Table VI, the reported incidence in negroes in San Francisco is fairly high in this survey. Because 83 per cent are males, the unmarried social status and the high percentage of physical laborers are expected (Table VI). The short duration in many cases is somewhat unusual, but these data probably refer to the time interval since the onset of symptoms and do not consider the fact that about 30 per cent of the subjects have probably had the disease itself for a period of more than five years (Table VIII). The high percentage of complete incapacity is not remarkable in a disease so rapidly fatal after the onset of symptoms (Table VII). No reported case was observed in a person

TABLE VII  
STATISTICAL SUMMARY  
(2,270 CASES REPORTED IN SECOND CITY-WIDE SURVEY)

GROUPS	CONGENITAL (%)	RHEUMATIC FEVER (%)	SYPHILIS (%)	THYROID (%)	SUBACUTE BACT. ENDOCARDITIS (%)	MISCELLANEOUS (%)	ARTERIO- SCLEROSIS (%)	HYPERTENSION (%)	FUNCTIONAL (%)	TOTAL (%)
<i>Functional Capacity</i>										
Ordinary physical ability	61.9	22.3	13.0	16.6	---	15.4	7.2	20.7	91.5	24.4
Slight limitation	18.6	28.4	26.0	38.7	21.4	15.4	24.4	25.2	6.8	23.0
Marked limitation	11.5	28.2	24.4	30.5	42.8	23.0	28.4	35.5	1.1	24.8
Complete phys. disability	8.0	21.1	36.6	14.2	35.8	46.2	40.0	18.6	0.6	27.8
Not stated	15.7	20.7	31.3	14.0	33.3	13.3	22.8	17.2	4.3	20.3
<i>Duration of Disease</i>										
Under 1 mo.	10.6	4.0	3.9	5.3	8.3	16.0	8.8	5.6	5.3	6.8
1 to 6 mo.	14.9	9.3	28.9	10.6	25.0	16.0	20.0	15.9	26.4	17.3
7 to 11 mo.	2.1	1.7	5.4	5.3	---	---	3.5	6.5	5.3	3.4
1 yr. to 2 yr.	8.5	9.6	11.7	13.3	25.0	12.0	18.6	18.7	20.9	14.9
2 yr. to 3 yr.	6.4	8.7	15.6	10.6	8.3	4.0	13.8	12.3	5.3	11.7
3 yr. to 4 yr.	2.1	8.5	9.4	10.6	---	12.0	6.3	13.0	15.8	7.9
4 yr. to 5 yr.	6.4	5.1	4.7	10.6	8.3	12.0	6.0	2.8	5.3	5.6
5 to 9 yr.	19.2	17.0	10.2	21.3	25.1	4.0	14.1	17.7	10.4	15.0
10 yr. and over	29.8	36.1	10.2	13.4	---	24.0	8.9	7.5	5.3	17.4
Indefinite—not stated	64.8	25.2	28.5	33.3	42.8	44.4	38.4	34.3	89.7	40.3

under the age of twenty years, and the peak of frequency, as expected, was in the fifth and sixth decades of life (Table VIII). The report of 3 per cent of auricular fibrillation (Table V), an extremely high figure for known cases of syphilitic heart diseases, leads one to believe that either arteriosclerosis or the rheumatic fever virus may have caused the heart damage in these cases, and a superimposed positive Wassermann reaction led to an erroneous diagnosis. The frequency of occurrence of valvular lesions (aortic and relative mitral insufficiency), angina pectoris, and auriculoventricular heart-block is not remarkable.

TABLE VIII  
AGE DISTRIBUTION  
(2,270 CASES REPORTED IN SECOND CITY-WIDE SURVEY)

GROUPS	ENTIRE POP. (%)	CONGENITAL (%)	RHEUMATIC FEVER (%)	SYPHILIS (%)	THYROID (%)	SUBACUTE BACT. ENDOCARDITIS (%)	MISCELLANEOUS (%)	ARTERIOSCLEROSIS (%)	HYPERTENSION (%)	FUNCTIONAL (%)	TOTAL (%)
Under 5 yr.	5.1	21.0	1.3	---	---	---	---	---	---	5.5	2.0
5-9 yr.	5.9	30.8	6.4	---	---	---	4.6	---	0.6	19.2	5.0
10-14 yr.	5.7	22.6	11.1	---	---	---	4.6	---	---	38.5	7.1
15-19 yr.	6.7	10.5	10.8	---	---	25.0	4.5	---	---	25.2	5.3
20-24 yr.	9.4	3.0	8.9	0.6	7.3	10.0	6.8	0.1	1.2	0.5	2.7
25-29 yr.	10.2	4.5	9.2	1.7	1.8	10.0	4.5	0.1	2.5	1.6	3.0
30-34 yr.	9.8	0.8	8.3	1.7	7.3	5.0	4.6	0.4	3.0	0.5	2.7
35-44 yr.	18.3	5.2	18.1	14.6	21.8	25.0	18.2	5.0	12.3	3.0	9.9
45-54 yr.	14.1	---	14.2	30.3	23.6	20.0	20.4	20.7	30.0	3.5	18.2
55-64 yr.	8.3	0.8	7.6	36.5	25.5	5.0	25.0	34.6	20.3	1.0	21.8
65-74 yr.	4.0	0.8	3.2	11.8	12.7	---	6.8	28.9	26.4	1.5	16.3
75 yr. or over	1.3	---	0.9	2.8	---	---	---	10.2	3.7	---	4.9
Unknown	1.3	0.7	0.2	0.6	0.4	4.8	2.2	1.8	---	1.0	1.2

The incidence of thyroid heart disease shows an unusual discrepancy between the controlled and uncontrolled divisions of this survey (Table IV). The figure for the total resembles the figures obtained in other surveys. Perhaps the difference can be interpreted as due to a variable degree of diagnostic acuity in the two groups of physicians reporting. The recognized predominance of females over males is shown also in our figures, in which a ratio of nearly 4 to 1 exists (Table V). Many of the patients were nonresidents. Auricular fibrillation, occurring in 17 per cent of these patients, and hypertension, occurring in 26 per cent of the cases, are common complications. Functional capacity was appreciably high. The incidence of valvular involvement to the extent of 42 per cent probably represents relative valvular insufficiencies. The age distribution (Table VIII, through middle life confirms the belief that there is a good possibility that coronary arteriosclerosis to some degree is not infrequently an accompanying factor in severe thyrotoxic disease.

Of the 33 cases of subacute bacterial endocarditis, 19, or 58 per cent, had rheumatic heart disease and 2, or 6 per cent, had congenital heart disease. Eighteen per cent of the patients are reported as having auricular fibrillation (Table V), which is far above the common experience, and 41.7 per cent of the cases were reported as over two years in duration (Table VII). The former finding is difficult to explain unless some of these were cases of recurrent subacute rheumatic heart disease, or cases of streptococcic septicemia of other types than *Streptococcus viridans*. The unusual number of prolonged cases of the disease is probably due to a misunderstanding by the reporting physician who gave the duration of the underlying rheumatic or congenital heart disease rather than that of the active endocarditis. The age distribution is characteristically in late youth and early middle life (Table VIII), and the selection by occupation, social and racial status is not remarkable, except the apparently high incidence in the negro (Table VI). It is unwise to attempt to draw further conclusions from such a small series of cases.

In the "hypertension" group (Table IV) it is remarkable that 6.8 per cent of the total are reported without note of obvious arteriosclerotic involvement of the coronary arteries. Probably these cases should be disregarded as a separate group since there is reported in Table V the occurrence of congestive failure, angina pectoris, and auricular fibrillation, which must represent coronary arteriosclerosis in some of these patients. In other respects, this group parallels the characteristics of the coronary arteriosclerotic group. Other than the hypertension group just discussed (Table IV), 36 per cent of the cases in the arteriosclerotic group have recognized hypertension as a secondary diagnosis. Thus of all cases of arteriosclerotic and hypertensive heart disease in this series, 46 per cent have recognized hypertension underlying the coronary arteriosclerosis. This is lower than the estimate of Fahr<sup>21</sup> that 75 per cent of all patients with coronary arteriosclerosis have or have had hypertension. Our figure of 46 per cent does not include a minor figure, 1.6 per cent of the reported cases that had hypertension as a complication of rheumatic, thyroid, or syphilitic heart disease.

The "coronary arteriosclerosis" group, constituting with the hypertension group 46.4 per cent of all reported cases, has a frequency approximating the incidence reported in other surveys. This is the group which represents the greatest apparent recent increase in heart disease in the United States. As stated by Cohn<sup>22</sup> and others, this is not only due to the saving of lives from infectious diseases in the early decades, but also to the recent downward trend in diagnoses by practicing physicians, of other degenerative diseases, such as arterial disease, including cerebral thrombosis, chronic nephritis, cerebral hemorrhage, and senility. These trends are illustrated for San Francisco by Table IX, showing the aging population, and by Fig. 1, in which

TABLE IX

## SAN FRANCISCO: AGE COMPOSITION OF POPULATION

YEAR	UNDER 45 YR.	45 YR. AND OVER
1910	80%	20%
1920	76%	24%
1930	72%	28%

there is a definite increase in heart disease as a cause of death during the last decade, but practically no change, and even a slightly downward curve, in the combined group comprised of all degenerative diseases. This is likewise shown in Table X, where the heart disease death

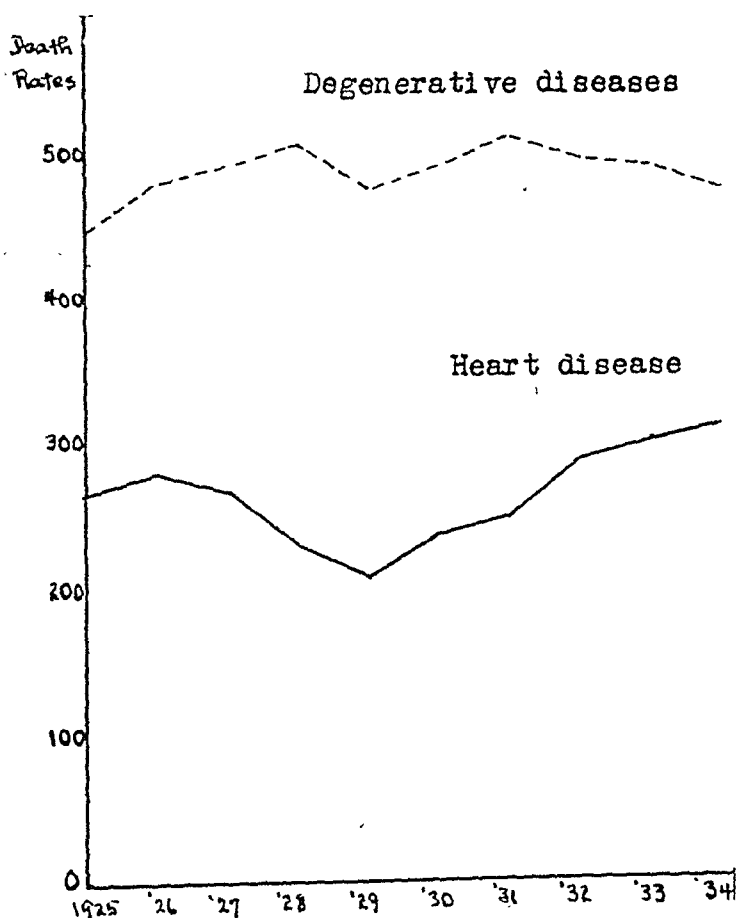


Fig. 1.—San Francisco—mortality from degenerative diseases, and heart disease 1925 to 1934.

rates for the younger ages decrease in 1924 and 1934, whereas the death rates for all ages increase from 259.6 to 316.7 per 100,000 population. Again the influence of an aging population on such crude death rates is shown on comparison of these data with standardized rates (Table XI), in which an adjustment has been made to the standard population age distribution.<sup>23</sup>

A review of Table V shows no unusually high frequency of family history of heart disease in the "coronary arteriosclerosis" or "hypertension" groups. The incidence of 11 per cent of angina pectoris in the former group agrees with most of the other surveys, as does the 12 per

cent of auricular fibrillation and the 3 per cent of heart-block. The rather low incidence of hypertension among Orientals (but high among negroes) is of interest. For closely similar age distributions in the hypertension and the arteriosclerosis groups the degree of incapacity is higher, perhaps, in the latter, than might be expected (Table VII). It is noted, also, that a rather high proportion of these patients are engaged in occupations requiring physical labor (Table VI).

TABLE X  
HEART DISEASE IN SAN FRANCISCO, 1924-1934  
(SPECIFIC DEATH RATES PER 100,000 IN AGE GROUPS)

AGE GROUPS	MALE				FEMALE			
	1924		1934		1924		1934	
	DEATHS	RATE	DEATHS	RATE	DEATHS	RATE	DEATHS	RATE
Under 35 yr.	46	28.1	32	18.0	43	28.02	31	17.0
35-44 yr.	44	73.2	92	133.9	35	75.1	36	63.3
45-54 yr.	123	294.2	251	465.4	65	208.7	73	171.4
55-64 yr.	215	967.6	329	1069.3	118	662.2	176	678.8
65-74 yr.	271	2987.9	351	2435.1	130	1538.09	270	2027.4
75 yr. or over	186	6092.3	259	6209.6	187	5216.1	274	5766.0
Unknown	1	38.9	---	---	---	---	---	---
All ages	886	293.06	1314	359.16	578	220.9	860	268.29
Total deaths (Heart disease)	1924—1464 Rate: 259.6				1934—2174 Rate: 316.72			

TABLE XI  
CRUDE AND STANDARDIZED DEATH RATES HEART DISEASE IN SAN FRANCISCO  
(PER 100,000 POPULATION)

YEAR	CRUDE RATE	STANDARDIZED RATE*
1930	241.88	255.49
1933	305.43	271.26

\*Population of England and Wales, 1921 Whipple Vital Statistics, Second Edition, Pages 192, 193; 296, 297.

The greater frequency of females in the uncomplicated hypertension classification, as compared to the higher incidence of males in the "arteriosclerosis" group might be explained by delayed production of symptoms in the more sedentary life of the women (Table V).

The percentage of cases of functional heart disease reported was not high, even in the private practice group, probably because they were excluded as cases of true heart disease. Of those reported 88.4 per cent were in persons under the age of twenty years (Table VIII), a fact perhaps satisfactorily explained on the basis of the circulatory instability of the adolescent period, especially with the large numbers reported from the Department of Public Health School Cardiac Diagnostic Center.

#### SUMMARY

The etiological classification of 3,535 cases is presented, divided into three brackets, namely, the private hospital and office patients of physicians of known diagnostic ability; the patients from two well-con-

trolled cardiac out-patient clinics; and a city-wide group of patients reported from hospitals and offices by an uncontrolled group of physicians of San Francisco, on an order of the Director of Public Health making heart diseases and the rheumatic fever syndrome reportable for fifteen months. Consideration is given to the reliability of the data.

The data from 2,270 cases reported during the last year of the San Francisco Health Department survey, and in many instances from the whole 3,535 cases, have been assembled for detailed study. This includes for the various etiological groups the incidence of sex, race, age, residence in San Francisco, marital status, occupation, familial heart disease, valvular involvement, congestive heart failure, angina pectoris, auricular fibrillation, auriculoventricular heart-block, functional capacity, and duration of disease.

A comparison is made between findings in the survey reported herein and those of others previously reported by various authors. The most interesting conclusion drawn was that, in San Francisco where the acute rheumatic fever syndrome is uncommon, the general incidence of rheumatic heart disease is approximately the same as that seen in private practice in Boston and New York, although definitely lower than in clinic practice in these eastern centers of population.

NOTE.—The survey of the rheumatic fever syndrome without rheumatic heart disease was unsatisfactory. Only fifty-one cases were reported having acute rheumatic fever, chorea, and/or growing pains without valvular heart disease in the 3,141 reports to the Department of Health.

#### REFERENCES

1. Hamilton, B. E., Hallesey, J. E.: 500 Cases, Boston City Hospital Outpatient Heart Clinic, Boston M. & S. J. 187: 139, 1922.
2. Wyckoff, J., Lingg, C.: Etiology in Organic Heart Disease, AM. HEART J. 1: 446, 1926.
3. Wood, J. E., Jr., Jones, T. D., Kimbrough, R. H.: Etiology of Heart Disease, Am. J. M. Sc. 172: 185, 1926.
4. Shane, C. T., Van Zant, F. R.: Heart Disease as Seen in a Southern Clinic, J. A. M. A. 59: 1473, 1927.
5. Benjamin, J. E.: Heart Disease Situation in Cincinnati, AM. HEART J. 2: 637, 1927.
6. Myers, M. M., Peck, J. H.: Chest Clinics in Iowa, AM. HEART J. 3: 287, 1928.
7. White, P. R., Jones, T. D.: Heart Disease and Disorders in New England, AM. HEART J. 3: 302, 1928.
8. Coffen, T. H.: Incidence of Heart Disease in Pacific Northwest, AM. HEART J. 5: 99, 1929.
9. Viko, L. E.: Heart Disease in the Rocky Mountain Region, AM. HEART J. 6: 264, 1930.
10. De Porte, J. V.: Heart Disease in General Medical Practice (In New York State), AM. HEART J. 3: 476, 1933.
11. Gager, L. T., Dunn, W. L.: Heart Disease in Washington, D. C., M. Ann., District of Columbia 2: 112, 1933.
12. Laws, C. F.: Etiology of Heart Disease in Whites and Negroes in Tennessee, AM. HEART J. 8: 608, 1933.
13. King, Robert L.: Heart Disease in the Pacific Northwest (Seattle), Northwest Med. 34: 154, 1935.
14. Maher, C. C., Sitler, W. W., Elliott, R. A.: Heart Disease in Chicago Area: A Study of Etiologic Factors in 1,000 Cases, J. A. M. A. 105: 263, 1935.
15. Moore, A. G.: Incidence of Heart Disease in 297 Cases, J. Indiana M. A. 28: 419, 1935.



16. Seegal, H., Seegal, B. C.: Studies in Incidence of Rheumatic Fever, J. A. M. A. 89: 11, 1927.
17. Seegal, H., Seegal, B. C., Jost, E. L.: A Comparative Study of Geographic Distribution of Rheumatic Fever, Scarlet Fever and Acute Glomerulonephritis in North America, Am. J. M. Sc. 190: 383, 1935.
18. Dauer, C. C.: Mortality Rates of Organic Diseases of the Heart by Geographical Areas in the United States, AM. HEART J. 10: 955, 1935.
19. Hedley, O. F.: A Study of 450 Fatal Cases of Heart Disease Occurring in Washington, D. C., Hospitals During 1932, Pub. Health Rep. 50: 1127, 1935.
20. Hedley, O. F.: A Critical Analysis of Heart Disease Mortality With Special Reference to Etiology, Race, and Sex, J. A. M. A. 105: 1405, 1935.
21. Fahr, George: The Heart in Hypertension, J. A. M. A. 105: 1396, 1935.
22. Cohn, A. E.: An Analysis of the Apparent Increase in the Heart Diseases, J. A. M. A. 105: 1394, 1935.
23. Whipple, George C.: Vital Statistics, England and Wales Standard Million, ed. 2, pp. 192, 193; pp. 296, 297, New York, 1923, John Wiley and Sons, Inc.

## RHEUMATIC FEVER IN NORTHERN CALIFORNIA\*

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**I**T IS a common observation among western clinicians that rheumatic fever and heart disease are usually rare and that the rheumatic infection itself is of milder nature than that seen in England or in the eastern United States. Some explanation for this impression should be advanced, but strangely enough is not available in the medical literature.

An analysis of two groups of cases was undertaken to determine the true incidence of the disease.

The first group was examined at the Cardiac Center of the San Francisco Department of Health.<sup>1</sup> The survey of data for this group reveals one outstanding feature—the incidence of congenital heart disease is surprisingly high in San Francisco school and preschool children. Fifty per cent of all organic lesions are those of congenital heart disease. This percentage is a marked contrast to the 12 to 20 per cent usually quoted in statistics from the East. The conclusion to be drawn from these figures is that because there is no valid reason why congenital heart disease should be more frequent in San Francisco than in Boston, the incidence of rheumatic fever must be correspondingly low. This impression has been corroborated by Richter<sup>2</sup> and by Sampson.<sup>3</sup>

Observations of the second group were made between October, 1930, and October, 1935, on 117 patients admitted to the pediatric wards of the San Francisco and University of California Hospitals and to the Children's Heart Clinic of the University of California Out-Patient Department. Complete studies including roentgenograms, fluoroscopy and electrocardiograms were made whenever possible. The same studies were made in the out-patient department group, though for obvious reasons without the completeness possible for hospitalized patients. Follow-up work has been done during the entire five-year period and has materially aided the diagnosis. The follow-up visits are made by the nurses assigned by the Visiting Nurses' Association to cardiac cases.

I have tried to compare my findings with those reported by workers in England and in northeastern United States in an effort to interpret the results of this study. Comparisons with local figures are practically impossible for studies of this type have not been attempted in northern California. This is a statistical summary, but it is hoped that the figures will prove interesting and will call attention to the status of rheumatic infection in California.

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*Hospital Incidence (Table I).*—It is somewhat surprising to find the hospital incidence of rheumatic infections relatively high in a community where the disease incidence has been observed to be low as is substantiated by the available epidemiological data on school children. The data in Table I reveals the hospital incidence to be double or triple that of similar general and teaching hospitals elsewhere, and even the pediatric wards, which always have a high percentage of infants, have a remarkably high incidence of rheumatic infection. The reasons for this discrepancy will not be apparent without further epidemiological study, but the answer may be among the following: First, the hospital incidence is markedly increased by the numbers of people who emigrate to California for their health. However, this explanation is partially refuted by the low incidence of rheumatic infection in Los Angeles. Second, the low school

TABLE I  
HOSPITAL INCIDENCE

HOSPITAL	PERCENTAGE OF TOTAL MEDICAL CASES OF RHEUMATIC FEVER AND CHOREA
Johannesburg, South Africa (European patients <sup>4</sup> )	5.80
Glasgow Royal Infirmary, Scotland <sup>4</sup>	4.74
University of California Medical Service	3.79
San Francisco Hospital <sup>4</sup>	3.75
University of California Pediatric and Medical Services	3.44
London Hospital, England <sup>4</sup>	2.75
University of California pediatric wards	2.50
Bellevue, New York <sup>4</sup>	1.50
Peter Bent Brigham, Boston <sup>4</sup>	1.30
Barnes, St. Louis <sup>4</sup>	0.47
Los Angeles County General <sup>4</sup>	0.44
University Hospital, Augusta, Georgia <sup>4</sup>	0.08

incidence and the high hospital incidence may indicate that we are dealing with forms of rheumatic infection, which after an apparently typical onset and course become benign and are not recognizable in routine school examinations. This seems a probable explanation and is one which is applicable to scarlet fever, which by epidemiological fact, is more benign in California. The second explanation appears the more likely in view of the evidence which will be presented.

*Family History (Table II).*—Family influence is well recognized in the rheumatic infection and has been observed by many in this country and in Europe. Whether this represents a distinct contagious element, inheritance of the susceptibility, transference of an obscure immunological response from mother to child, or the presence of some dietary deficiency in the whole family, as suggested by Rinehart,<sup>5</sup> is a matter for sufficient speculation to intrigue a corps of experimental and epidemiological workers. An understanding of the rôle of these factors will do much to solve the etiological puzzle. A positive family history is present in 32.4 per cent of my 116 cases, which corresponds to the 29 per cent reported

by St. Lawrence<sup>6</sup> in this country and the 40 per cent reported by Poynton and his associates.<sup>7</sup> The agreement with the figure of Findlay<sup>8</sup> (34.7 per cent) is obvious in Table II.

TABLE II  
RHEUMATIC INFECTION—POSITIVE FAMILY HISTORY

PLACE OBSERVED	PATIENTS	PATIENTS WITH POSITIVE FAMILY HISTORY	PERCENTAGE POSITIVE FAM- ILY HISTORY
University of California Pediatric Department	46	15	32.6
University of California Children's Cardiac Clinic	47	16	34.0
San Francisco Hospital Pediatric ward	23	6	28.8
<i>Total</i>	116	37	32.4
Leonard Findlay's Surveys	701	243	34.7

*Sex Incidence (Tables III and IV).*—Sex incidence is hardly to be considered of epidemiological importance, and yet a widely known fact is that the rheumatic infection occurs slightly more frequently in the female than in the male as is shown in Table III.

TABLE III  
RHEUMATIC INFECTION—SEX INCIDENCE

PLACE OBSERVED	PATIENTS	MALE	FEMALE
University of California Pediatric Department	46	16	30
University of California Children's Cardiac Clinic	47	24	23
San Francisco Hospital Pediatric Ward	23	16	7
<i>Total</i>	116	56	60
Ratio Male to Female {		San Francisco	1:1.07
		Findlay	1:1.09

Table IV also reveals that chorea is at least two and a half times more frequent in girls than in boys, an observation which is fairly constant throughout the world.

TABLE IV  
CHOREA: SEX INCIDENCE

PATIENTS	MALE	FEMALE	RATIO	
			SAN FRANCISCO	FINDLAY
28	8	20	1:2.5	1:2.8

*Age Incidence (Fig. 1).*—Numerous recent reports are available in the literature to refute the old idea that rheumatic fever does not occur before the third year. Noteworthy among these reports is that of McIntosh and Wood.<sup>9</sup> Findlay<sup>8</sup> does not report a patient whose onset was under three years of age and my series includes no case recognized before three years of age. Yet there were observed, in my service of 106 con-

secutive rheumatic children under twelve years of age, 14 children in whom the onset was before five years of age. This constitutes 13.2 per cent as compared with 12 per cent reported by Poynton<sup>10</sup> in a similar age group.

Figure 1 is a graphic representation of the age incidence in my group and Findlay's.<sup>8</sup> Although mine is a much smaller group, the similarity in the curves is remarkable, both reaching their peak at seven years of age and falling rapidly to fourteen years of age. In Findlay's series,

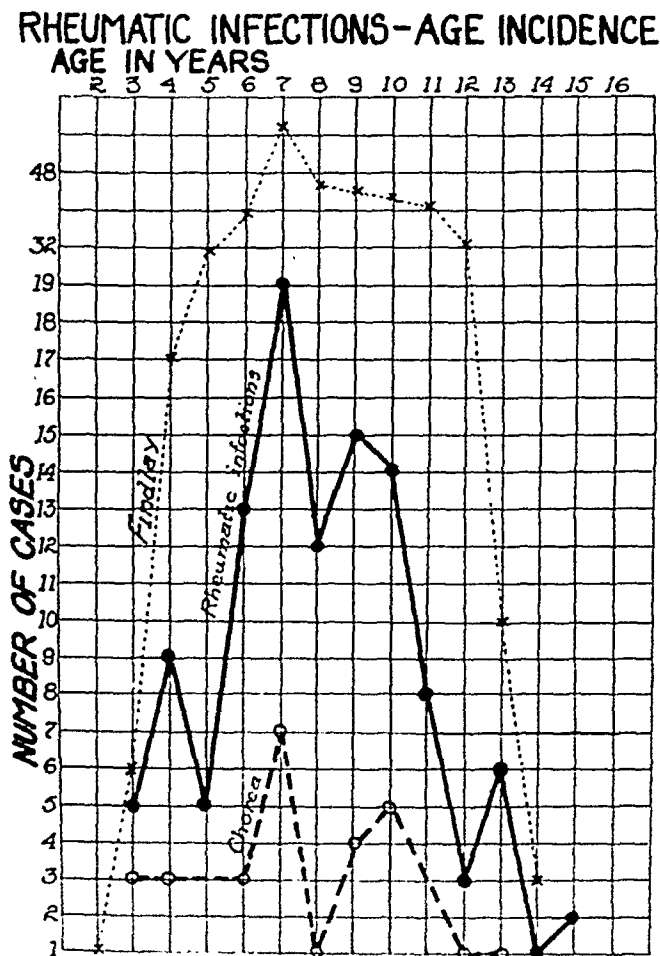


Fig. 1.

52.2 per cent occurred between the seventh and tenth years, Fig. 1 reveals that 54.5 per cent occurred in the same period in the northern California series.

The value of the information is twofold. First, our diagnostic ability is improved by knowledge of time of onset; and second, although rheumatic disease undoubtedly tends to increase in incidence after five years of age, onset of the disease before that time is of considerable prognostic importance. Carditis is most likely to occur in the young and is likely to be severe and even fatal in those under five years of age.

*Seasonal Incidence (Fig. 2).*—The scope of this paper does not warrant a discussion of the climatology of the rheumatic infection as that factor presents an epidemiological problem in itself. The geographical distribution and the fact that rheumatic fever in the tropics is practically absent is well known. The various factors involved in this distribution are not well understood; but, since it is known that dampness and chilling constitute two major contributory factors, it is not difficult to realize why the peak in the northeastern section of this country occurs during

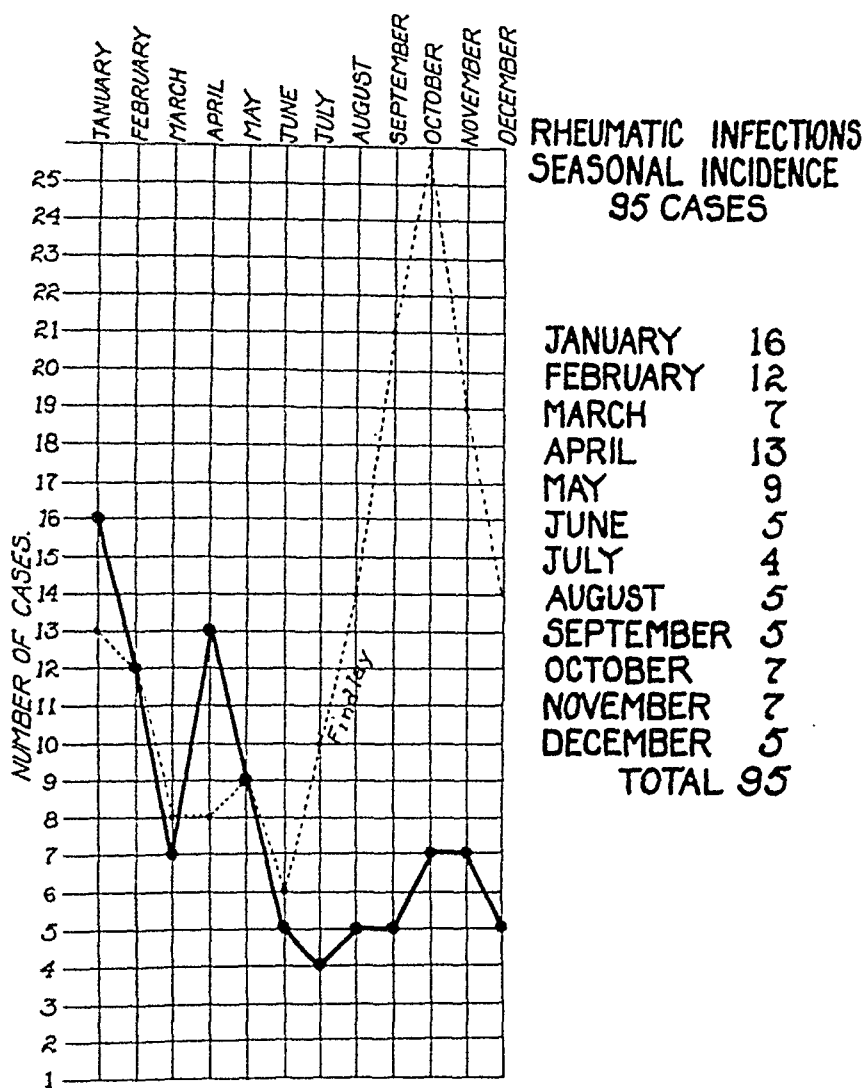


Fig. 2.

the first three to four months of each year, while that in the British Isles occurs in September, October and November. A study of vital statistics<sup>11</sup> seems to substantiate this assumption.

A surprising peak in onset incidence in northern California following a cold and damp December, January, and February is shown in Table V, and I believe this undoubtedly accounts for the difference in incidence between Findlay's seasonal incidence curve and that of northern California. It can only be surmised what benefit these facts are in determining the etiology of rheumatic fever. Whether the cold damp season, with

its increased incidence of respiratory infections, implies an infectious etiology because of changing blood supply of tissue, or whether the general susceptibility of the body is lowered, are questions which continue to intrigue the immunologist and clinician.

TABLE V

AVERAGE MEAN TEMPERATURE BY MONTHS FOR YEARS 1932, 1933, AND 1934 IN SAN FRANCISCO

Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
49.3	52.7	57.7	56.8	58.0	59.2	59.7	60.5	62.6	62.1	59.7	50.2

AVERAGE PRECIPITATION IN INCHES BY MONTHS FOR YEARS 1932, 1933, AND 1934 IN SAN FRANCISCO

Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
3.31	2.93	1.28	0.34	0.71	0.24			0.09	0.79	1.58	3.66

*The Rheumatic Infection—Types of Onset (Tables VI and VII).—*The manifestations of rheumatic infection at the onset vary widely: each type is illustrated in the accompanying Table VI. The manifestations at onset can be divided into those of primary and secondary importance, with polyarthritides, chorea, carditis, and subcutaneous nodules comprising the former. Because tonsillitis was present in such a high percentage of my cases, I would like to include this among those manifestations of greatest importance. Scarlet fever, erythema, growing pains, extrasystoles, abdominal pain, and purpura are of secondary importance. Pathologically, each of these manifestations has been adequately explained and in most cases is correctly correlated with the rheumatic infection. Coombs,<sup>12</sup> and later Coburn,<sup>13</sup> covered this phase so well that little can be added.

Table VI also illustrates a remarkable similarity between the rheumatic infection of the eastern United States and that of northern California. The cases observed by Coburn, with the exception of carditis, are strikingly comparable with mine. This is a significant fact and, I believe,

TABLE VI

RHEUMATIC INFECTION—TYPES OF ONSET IN 116 PATIENTS

TYPE OF ONSET	OCCURRENCE	PERCENTAGE	COBURN
Arthritis	79	68.1	71.5
Chorea	32	27.5	23.4
Carditis	24	20.6	64.8
Tonsillitis	22	18.9	*
Nodules	12	10.3	13.0
Scarlet fever	9	7.7	7.3
Erythema	7	6.0	17.0
Growing pains	5	4.0	46.8
Extrasystoles	2	1.7	*
Abdominal pain	1	0.8	19.0
Purpura	1	0.8	6.7
Total	194		

\*Not noted.

tends to substantiate my suggestion that in San Francisco we deal with a relatively benign type of rheumatic infection, when measured in terms of cardiac damage resulting from the rheumatic infection. This becomes more apparent with study of Table VII when the associated rheumatic manifestations are tabulated and compared with Findlay's figures.<sup>8</sup> This table represents combinations of different rheumatic manifestations and their accompanying carditis. When the problem is approached in this way, the revelation is startling in that with the several combinations noted, carditis is less frequent to a marked degree, although the presence of carditis occurring alone is about the same. The latter fact probably means that the recognition was accurate.

TABLE VII

ASSOCIATED RHEUMATIC MANIFESTATIONS: TYPES OF ONSET ONLY

MANIFESTATION	NUMBER	PERCENTAGE WITH CARDITIS	PERCENTAGE WITH CARDITIS (FINDLAY)
Arthritis	52	13.8	75.1
Arthritis and carditis with growing pains	7		
Arthritis, carditis, and nodules	2		
Arthritis and nodules	4	11.1	53.6
Chorea	13		
Chorea and nodules	3		
Chorea and carditis	1	20.2	69.2
Chorea, carditis, and nodules	1		
Arthritis and chorea	11		
Arthritis, chorea, and carditis	1	9.2	4.1
Arthritis, chorea, carditis, and nodules	2		
Arthritis, chorea, and nodules	1		
Carditis	10		
<i>Total</i>	108		

*Rheumatic Infection: Cardiac Lesions—Clinical Frequency in 81 Patients (Table VIII).*—Another similarity between the rheumatic infection in San Francisco and elsewhere is illustrated by Tables VIII and IX which reveal the cardiac lesion both when occurring alone and in combination with other lesions of rheumatic fever. The outstanding differences in these tables are in the smaller number of patients who had evidence of mitral insufficiency and mitral stenosis, and in those

TABLE VIII

RHEUMATIC INFECTION: CARDIAC LESIONS—CLINICAL FREQUENCY IN 81 PATIENTS

TYPE OF LESION	PATIENTS	PERCENTAGE	PERCENTAGE (FINDLAY)
Mitral regurgitation	72	88.8	96.8
Mitral stenosis	18	22.2	42.1
Aortic regurgitation	14	17.2	12.0
Pericarditis	10	12.3	14.1
Aortic stenosis	5	6.1	*
Tricuspid insufficiency	1	1.2	*
<i>Total</i>	81		
No demonstrable lesion	35	30.0	3.2
<i>Total patients</i>	116		

\*Not noted.



TABLE IX

RHEUMATIC INFECTION: FREQUENCY OF ASSOCIATED VALVULAR LESIONS IN 73 PATIENTS

TYPE OF LESION	NUMBER	PERCENTAGE	PERCENTAGE (FINDLAY)
Mitral regurgitation	42	57.5	45.6
Mitral regurgitation and stenosis	8	10.9	29.2
Mitral regurgitation, stenosis, aortic regurgitation	7	9.5	4.2
Mitral regurgitation, stenosis, aortic regurgitation, pericarditis	1	1.3	1.6
Mitral regurgitation, stenosis, pericarditis	3	4.1	6.1
Mitral regurgitation, pericarditis	6	8.2	3.6
Mitral regurgitation, aortic regurgitation	1	1.3	3.8
Mitral regurgitation, aortic regurgitation, pericarditis	1	1.3	2.0
Mitral stenosis	0	0.0	2.4
Mitral stenosis, aortic regurgitation	0	0.0	0.2
Aortic insufficiency	4	5.4	5.9
<i>Total</i>	73		

which show no demonstrable cardiac pathology when studied by modern methods of clinical and laboratory approach. I realize that the majority of Findlay's cases were studied over a longer period than five years, while the San Francisco series was studied for about two and a half years. This difference in follow-up period partly accounts for the lower percentage of mitral insufficiency, mitral stenosis, and demonstrable cardiac pathology in my tables. However, I believe it is worth noting that with as high a percentage as 30, I am unable to demonstrate clinical or laboratory evidence of cardiac involvement. I realize that though the cards have been shuffled and dealt for this potential cardiac group, the score has not been added. Nevertheless, I present it as further evidence that in San Francisco we deal with a type of rheumatic fever which is of a peculiarly benign nature. I have only suggested the factors influencing this, leaving the truth or fallacy to be decided by further epidemiological study.

Finally, it is also apparent that when the infection does occur, with the exception of the above mentioned mildness, it bears a remarkable similarity to the rheumatic infection elsewhere, as exemplified by family history, age, and seasonal incidence and types of onset and of cardiac involvement.

## SUMMARY

A study of rheumatic fever in northern California reveals an unusually high hospital incidence and a low general incidence. A possible explanation which this study of 116 cases in San Francisco brings out is that, while the percentage of cases with no demonstrable cardiac pathology is 30, the incidence of carditis in combination with other rheumatic manifestations is correspondingly low. This suggests that we are dealing with a benign type of rheumatic infection comparable with that of other communicable diseases in California.

In all other respects the rheumatic infection is identical with that seen in the eastern part of the country and in the British Isles.

There was a positive family history for rheumatic fever in 32.4 per cent of this series. The ratio of female to male shows a slight predominance of the former. In chorea the ratio is 2.5 to 1. The peak of the age incidence curve is seven years, and 54.5 per cent of the cases occur between the seventh and tenth years.

In San Francisco the rheumatic infection is a disease which occurs during the first four months of each year. Climatological data are presented which show that in San Francisco December, January, and February are usually the cold and damp months. Types of onset of the rheumatic infection are similar to those of rheumatic fever in the eastern United States. This series includes all the more common types of onset and some of the rarer ones.

#### REFERENCES

1. Christie, A.: Incidence and Type of Heart Disease in San Francisco School Children and Its Relation to the Rheumatic Fever Problem. Part II Completed for Publication.
2. Richter, I. M.: Incidence and Variety of Heart Disease in School Children of San Francisco, *J. A. M. A.* 97: 1060, 1931.
3. Sampson, J. J.: Incidence and Type of Heart Disease in San Francisco School Children and Its Relation to the Rheumatic Fever Problem. Part I. In Preparation.
4. Faulkner, J. M., and White, P. D.: The Incidence of Rheumatic Fever, Chorea, and Rheumatic Heart Disease, *J. A. M. A.* 83: 425, 1924.
5. Rinehart, J. F.: Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis; Experimental, Clinical, and General Considerations. I. Rheumatic Fever; *Ann. Int. Med.* 9: 586, 1935.
6. St. Lawrence, W.: The Family Association of Cardiac Disease, Acute Rheumatic Fever, and Chorea, *J. A. M. A.* 79: 2051, 1922.
7. Poynton, F. J., Paterson, D., and Spence, J. C.: Acute Rheumatism in Children, *Lancet* 2: 1086, 1920.
8. Findlay, L.: The Rheumatic Infection in Childhood, London, 1931, Edward Arnold & Co.
9. McIntosh, R., and Wood, C. L.: Rheumatic Infections Occurring in First Three Years of Life, *Am. J. Dis. Child.* 49: 835, 1935.
10. Poynton, F. J., and Schlesinger, B.: Recent Advances in Study of Rheumatism, Philadelphia, 1931, P. Blakiston's Son & Co., Inc.
11. World Weather Records: Clayton, Smithsonian Institute, 1927.
12. Coombs, C.: Rheumatic Heart Disease, Bristol, 1924, John Wright & Sons, Ltd.
13. Coburn, A.: The Factor of Infection in the Rheumatic State, Baltimore, 1931, Williams & Wilkins Company.

## RACIAL DIFFERENCES IN THE INCIDENCE OF CORONARY SCLEROSIS

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**S**TUDIES of the incidence of the various types of heart disease in cities having a relatively large negro population have demonstrated that in the negro both hypertensive heart disease and syphilitic heart disease are far more frequent than in white patients. Schwab and Schulze<sup>1</sup> found that in the negro hypertensive heart disease is two and one-half times more frequent and that syphilitic heart disease is four times as frequent as in white patients. Subsequently they called attention to the fact that in their patients 65 per cent of the negroes with hypertension were under the age of fifty years, whereas in the white patients 65 per cent of the cases occurred after this age.<sup>2</sup> Stone and Vanzant<sup>3</sup> also emphasized the greater incidence of both syphilitic and hypertensive heart disease in the negro, as well as the tendency of the latter disease to occur in negroes much earlier in life.

Sclerosis of the coronary vessels, however, would appear to be less frequent in the negro. Schwab and Schulze<sup>1</sup> found the incidence one and one-half times greater in their white patients, while Stone and Vanzant found the proportion of whites to negroes four to one. The former authors believe that the difference is due to the fact that a smaller number of negroes reach the period of life in which this type of heart disease occurs, and believe that in older negroes the incidence would be higher than in whites. They found no cases of angina pectoris among negroes and offer the same explanation as Roberts,<sup>4</sup> that it is because negroes seem to be less highly organized nervously. It is significant that Stone and Vanzant recorded all patients with high blood pressures among the hypertensive group, while Schwab and Schulze<sup>1</sup> stated that in their cases of arteriosclerotic heart disease the diastolic blood pressure was normal or very slightly elevated, whereas the systolic pressure was constantly high.

From clinical evidence alone, it is frequently impossible to determine in a given patient how much of the cardiac failure is secondary to hypertension, and how much is due to coronary sclerosis. The diagnosis of coronary sclerosis depends to a large extent upon the symptoms of which the patient complains, and these symptoms are notoriously rare in the negro race. It is not surprising, therefore, that this clinical diagnosis should be made less frequently in the negro, especially since the incidence of hypertension is much greater; so that one would expect to find many cases with marked coronary sclerosis classified clinically as cases of hypertensive heart disease.

Since clinical data alone will not suffice to show the relative incidence of coronary sclerosis among negroes and whites, it was thought that a study of autopsy records might give some information on the point in question. A study was made of the clinical and autopsy records of four hundred consecutive autopsies, one hundred each in white males and females and one hundred each in negro males and females, all patients being forty years of age or older, irrespective of the cause of death, in order to determine the presence and degree of sclerosis of the coronary vessels. This method of study cannot be regarded as highly accurate. Nevertheless, since each autopsy record contains a note by two examiners, it was hoped that a fair estimate might be obtained, which would be certainly more accurate than clinical impressions. From the clinical records note was also made of the Wassermann reaction and of the patient's blood pressure. In several cases patients were admitted in shock and died shortly after admission; many of these patients had been followed at intervals in ward and out-patient department for several months or years, and it was possible to obtain accurate information about blood pressure levels. In cases in which such information could not be obtained, however, the pressure levels of these moribund patients were disregarded. Sclerosis of the coronary vessels was graded "0" when there was no sclerosis or only a few yellow flecks of intimal fat deposit; "1" when there was noted moderate streaking with calcium; "2" when sclerosis was well marked but when no narrowing of the lumen of the vessel was present; and "3" when there was marked sclerosis and definite encroachment upon the lumen of either of the vessels. Decrease in the vascular lumen at any point was graded "3," even though the vessels elsewhere might be comparatively free of sclerosis, and the condition of that artery which showed the most advanced changes was taken as the criterion for classification. In cases in which definite evidence of coronary occlusion was present, the degree of sclerosis was, of course, grade 3, and a further note was made of the presence of the occlusion. For the sake of further comparison, patients were divided into two groups according to whether death occurred on a medical or a surgical service.

Tables I to IV show the results obtained in white males, negro males, white females, and negro females, respectively. Comparing the males we find that although there were considerably more negroes from the medical service, the incidence of marked coronary sclerosis among them was 9 per cent and of coronary occlusion 4 per cent (two cases in which the occlusion was old and two in which it was recent and the cause of death), whereas the figures for white males are 24 per cent and 9 per cent, respectively (four cases of old, four cases of recent occlusion, and one case with both an old and a recent occlusion). These differences can hardly be attributed to the slight difference in the average age of the two groups, which is more than compensated by the fact that 68 per cent

of the negro males died on the medical service, compared with 54 per cent of the white males. The larger number of white males from the surgical service would tend to decrease the apparent incidence of coronary sclerosis among the whites, more than among the negro males; thus, of the medical patients alone, the incidence of marked coronary sclerosis is 31.4 per cent for the white males and 12 per cent for the negro males.

TABLE I  
WHITE MALES

AGE GROUP	MEDICAL						SURGICAL						TOTAL PA-TIENTS
	CORONARY SCLEROSIS				OCCLU-SION	TOTAL	CORONARY SCLEROSIS				OCCLU-SION	TOTAL	
	0	1	2	3			0	1	2	3			
40-44	6	2	0	1	1	9	5	1	0	0	0	6	15
45-49	3	0	1	1	0	5	2	1	1	1	0	5	10
50-54	6	1	0	3	3	10	2	3	4	0	0	9	19
55-59	1	4	0	2	0	7	4	1	0	1	0	6	13
60-64	3	3	1	2	1	9	6	1	0	0	0	7	16
65-69	0	1	1	3	0	5	4	0	0	0	0	4	9
70-74	1	0	0	3	2	4	0	1	1	2	1	4	8
75-79	1	0	0	1	0	2	0	2	0	2	0	4	6
80+	0	1	1	1	0	3	0	0	0	1	1	1	4
Totals	21	12	4	17	7	54	23	10	6	7	2	46	100

Average age: 57.24 years

Average blood pressure: 51 medical patients,  $\frac{142.3}{85.1}$ ; 45 surgical patients,  $\frac{147.0}{88.3}$

Average of whole group (96 patients),  $\frac{144.5}{86.6}$

Syphilitic aortitis was found post mortem in four of the white males. In two of these cases coronary sclerosis was marked, one of them showing in addition gross myocardial scarring, but there was no evidence that either the coronary narrowing or the myocardial scarring was due to a syphilitic process. In the group of negro males syphilitic aortitis was found post mortem in twenty-eight cases. In four of these cases the orifices of the coronary arteries were markedly narrowed by the process in the aorta. Three of these showed slight and the fourth moderate coronary sclerosis in addition; they are so recorded in Table II in spite of the actual stenosis caused by the syphilitic process.

It is a well-established fact that coronary disease is less frequent in women than in men, and a comparison of Tables I and III shows only what one might expect if the method of study is reasonably accurate. Thus, in the present series, marked sclerosis was noted in 24 per cent of the white males and in 10 per cent of the white females; the figures for coronary occlusion are 7 per cent and 4 per cent, respectively. Comparing the white females with the negro males, however, we find that the incidence of coronary disease is about the same, being 10 per cent for the white females and 9 per cent for the negro males. Table IV would seem to indicate that there is the same sex difference in the incidence of

TABLE II  
NEGRO MALES

AGE GROUP	MEDICAL						SURGICAL						TOTAL PA- TIENTS
	CORONARY SCLEROSIS				OCCLU- SION 1 RECENT 2 OLD	TOTAL	CORONARY SCLEROSIS				OCCLU- SION	TOTAL	
	0	1	2	3			0	1	2	3			
40-44	7	3	1	0	0	11	8	0	0	0	0	8	19
45-49	11	2	1	3	1	17	4	1	0	0	0	5	22
50-54	4	5	0	3	2	12	2	0	0	0	0	2	14
55-59	10	2	1	1	0	14	4	0	2	0	0	6	20
60-64	6	1	1	0	0	8	0	1	0	0	0	1	9
65-69	1	2	0	0	0	4	1	1	0	0	0	2	6
70-74	0	1	0	0	0	1	0	2	3	0	0	5	6
75-79	1	0	0	0	0	1	1	1	0	1	1	3	4
Totals	40	16	4	8	3	68	20	6	5	1	1	32	100

Average age: 53.82 years

Average blood pressure: 63 medical,  $\frac{162.2}{95.2}$ ; 28 surgical,  $\frac{156.7}{86.7}$ Average of whole group (91 patients),  $\frac{160.5}{92.6}$ TABLE III  
WHITE FEMALES

AGE GROUP	MEDICAL						SURGICAL						TOTAL PA- TIENTS
	CORONARY SCLEROSIS				OCCLU- SION 3 RECENT 1 OLD	TOTAL	CORONARY SCLEROSIS				OCCLU- SION	TOTAL	
	0	1	2	3	0	1	2	3					
40-44	6	1	3	0	0	10	3	1	0	0	0	4	14
45-49	4	1	0	0	0	5	8	2	0	0	0	10	15
50-54	7	1	1	1	1	10	5	0	0	0	0	5	15
55-59	8	2	0	0	0	10	1	2	0	0	0	3	13
60-64	2	3	1	2	1	8	6	0	0	0	0	6	14
65-69	0	0	6	2	1	8	0	3	0	0	0	3	11
70-74	2	1	1	5	1	9	3	0	0	0	0	3	12
75-79	0	1	1	0	0	2	0	0	1	0	0	1	3
80+	0	1	0	0	0	1	1	1	0	0	0	2	3
Totals	29	11	13	10	4	63	27	9	1	0	0	37	100

Average age: 57.58 years

Average blood pressure: 59 medical,  $\frac{161.1}{90.6}$ ; 33 surgical,  $\frac{139.8}{81.6}$ Average of whole group (92 patients),  $\frac{153.5}{87.4}$ 

coronary disease among negroes as among whites and that negro females are accordingly less susceptible to coronary sclerosis than are any of the other three groups studied. Table V summarizes the results obtained in the study of the four groups.

The age distribution in the various groups may account for some of the differences noted in the incidence of coronary disease. The average

TABLE IV  
NEGRO FEMALES

AGE GROUP	MEDICAL						SURGICAL						TOTAL PA- TIENTS
	CORONARY SCLEROSIS				OCCLU- SION 1 RECENT 1 OLD	TOTAL	CORONARY SCLEROSIS				OCCLU- SION	TOTAL	
	0	1	2	3			0	1	2	3			
40-44	14	1	0	0	0	15	16	1	2	0	0	19	34
45-49	16	3	1	0	0	20	7	3	0	0	0	10	30
50-54	4	0	0	1	0	5	3	2	1	0	0	6	11
55-59	4	3	3	0	0	10	3	1	0	0	0	4	14
60-64	0	3	0	1	0	4	3	0	0	0	0	3	7
65-69	0	2	0	1	1	3	0	0	0	0	0	0	3
70-74	0	0	0	1	1	1	0	0	0	0	0	0	1
Totals	38	12	4	4	2	58	32	7	3	0	0	42	100

Average age: 48.78 years

Average blood pressure: 56 medical patients,  $\frac{172.7}{99.1}$ ; 36 surgical patients,  $\frac{149.9}{89.3}$

Average of whole group (92 patients),  $\frac{163.8}{95.3}$

age of the white males and females (57.24 and 57.58 years, respectively) is about the same, but the average age of the negro males (53.82 years) is approximately three and one-half years less, and of the negro females a full eight and one-half years less than that of the white males. One must also consider the fact that all of the negroes were public ward patients, whereas a certain proportion of the white patients were from the private wards; and, since coronary sclerosis is believed to be more frequent among the so-called "upper walks" of life, it is possible that the differences noted in the incidence of the disease are due to occupational rather than racial factors.

TABLE V

	MARKED CORONARY SCLEROSIS	OCCLUSION	SYPHILITIC AORTITIS	AVERAGE AGE, YEARS
White males—100	24	9	4	57.2
Negro males—100	9	4	28	53.8
White females—100	10	4	1	57.6
Negro females—100	4	2	12	48.8

Although the evidence herein presented is not entirely conclusive, it at least indicates that there may be definite differences in the incidence of coronary disease between members of the white and of the negro races. The etiological factors in the production of coronary disease are at present poorly understood; if faulty hygiene has any bearing upon the subject, one would expect the negro to be much the more susceptible.

## SUMMARY

A study of the autopsy records of four hundred patients above the age of thirty-nine years showed the incidence of marked coronary sclerosis to be 24 per cent for white males, 9 per cent for negro males, 10 per cent for white females, and 4 per cent for negro females.

Coronary occlusion with myocardial infarction, either recent or old, was found in 9 per cent of the white males, 4 per cent of the negro males, 4 per cent of the white females, and 2 per cent of the negro females.

The evidence suggests that members of the white race are much more susceptible to coronary sclerosis than are negroes.

## REFERENCES

1. Schwab, E. H., and Schulze, V. E.: The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary, *AM. HEART J.* 7: 223, 1931.
2. Schwab, E. H., and Schulze, V. E.: Heart Disease in the American Negro of the South, *AM. HEART J.* 7: 710, 1932.
3. Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic, *J. A. M. A.* 89: 1473, 1927.
4. Roberts, S. R.: Nervous and Mental Influences in Angina Pectoris, *AM. HEART J.* 7: 21, 1931.



# STUDIES ON EXPERIMENTAL CORONARY OCCLUSION\*†

## CHEMICAL AND ANATOMICAL CHANGES IN THE MYOCARDIUM AFTER CORONARY LIGATION

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THE experiments herewith recorded were designed to correlate histological and chemical changes in the myocardium as these are affected by permanent or temporary ligation of the coronary vessels. The chemical studies deal with the determination of the glycogen and lactic acid content of the muscle.

Preliminary reports from this laboratory have dealt with surface temperature<sup>1</sup> and chemical<sup>2</sup> changes in the myocardium, and electrocardiographic configurations<sup>3</sup> after ligation of the coronary vessels. Immediately after the ligation of the descending ramus of the left coronary artery the temperature of the affected muscle, measured by thermocouples and a Leeds & Northrop potentiometer recording system, dropped from 2 to 8° F. below the level of the muscle with its circulation intact, and with release of the ligature the temperature rose promptly to its former level. It was also shown that vagotomy, bilateral stellate ganglionectomy, stimulation of the vagi or of the sympathetic fibers to the heart had no effect on these temperature changes. The results indicate that, with the sudden deprivation of the blood supply, no immediate collateral circulation to the affected myocardium is developed.

### METHODS

Dogs weighing from 15 to 20 kilograms were anesthetized with sodium amytal and, under mild artificial respiration, the hearts were exposed either by resection of the fourth left rib or by a simple incision through the fourth left interspace. The anterior descending branch of the left coronary artery with its accompanying veins was ligated within 2 cm. of its origin. The pericardium and chest wall were then tightly closed and were reopened only to remove tissue for chemical analysis. The samples of tissue were excised from the beating heart in situ in the living animal and plunged immediately into liquid air; this procedure required not more than 15 seconds. Samples of tissue were removed from the zone supplied by the ligated vessels and from a control zone, the right ventricle, and were analyzed either for lactic acid or glycogen. About 2 gm. of tissue were employed for each determination. The frozen tissue was fragmented and put into weighing bottles containing sulphuric acid for lactic acid determinations by the method of Friedemann and Graesser.<sup>4</sup> For the glycogen determination the fragmented frozen tissue was placed in 50 c.c. centrifuge tubes containing 5 c.c. of 60 per cent potassium

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hydroxide. The hydrolysis was carried out by the modified Pflüger method as outlined by Yannet and Darrow,<sup>5</sup> and the glucose content was determined in aliquots by Somogyi's modification of the Shaffer-Hartman sugar method.

Immediately after the termination of the experiments the hearts were examined for gross changes in consistency and appearance of the myocardium, and the coronary arteries were carefully explored to determine whether the vessels were securely ligated or patent in the instances where the circulation was reestablished. Blocks of tissue were taken from the zone supplied by the ligated vessels as well as from the right ventricle, and these were fixed in 4 per cent formaldehyde and Zenker's fluid. Sections were stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, Mallory's aniline blue connective tissue stain, and sudan III.

#### EXPERIMENTAL DATA

*Chemical and Anatomical Changes After Ligation of Coronary Vessels.*—In this group of experiments the anatomical changes were correlated with the lactic acid or the glycogen changes in the myocardium of dogs whose coronary vessels had been ligated for periods ranging from one-half hour to twenty-four hours.

The lactic acid content of the muscle tissue from the zones supplied by the ligated vessels was strikingly increased in all instances as compared to that of the control zone (Table I). In contrast, the glycogen content was decreased in all instances in the muscle tissue from the zone supplied by the ligated vessels (Table II). Control animals subjected to the same surgical procedures but in whom the sutures were merely passed about the coronary vessels and then removed showed no significant variation in the lactic acid or glycogen content of the muscle tissue from the two zones.

TABLE I

LACTIC ACID CONTENT OF HEART MUSCLE AFTER LIGATION OF CORONARY VESSELS

DOG NO.	NO. OF HR. LIGATED	LACTIC ACID	
		AV. MG. /100 GR. OF TISSUE	
		INVOLVED ZONE	UNINVOLVED ZONE
45	½	149.5	47.5
44	4	193.5	58.0
42	10	96.5	54.0
43	24	97.8	61.8
46	24	51	51.2
	(Control)		

TABLE II

GLYCOGEN CONTENT OF HEART MUSCLE AFTER LIGATION OF CORONARY VESSELS

DOG NO.	NO. OF HR. LIGATED	GLYCOGEN AS GLUCOSE	
		AV. MG. /100 GR. OF TISSUE	
		INVOLVED ZONE	UNINVOLVED ZONE
47	2	503.0	826.0
75	4	296.0	1051.5
53	8	354.0	1410.0
51	24	490.5	1142.0
54	24	958.5	938
	(Control)		

The histological changes in the myocardium with occlusion of the coronary vessels varied with the period of ligation. They may be divided into two main groups, the first includes the first forty-eight-hour period when the necrotizing and exudative processes predominate, and the second, longer periods associated with the appearance of the reparative processes (Table V).

The earliest histological changes in the myocardium were seen in the preparations from dogs killed eight hours after ligation of the coronary vessels, and consisted of edema of the interstitial tissue and fat droplets in the cytoplasm of the myocardial fibers. In the preparations from dogs killed twenty-eight hours after ligation, necrosis of the myocardial fibers was observed, together with an increase in the fat in the cytoplasm of the cells and a polymorphonuclear cellular exudate and red blood cell infiltration throughout the interstitial tissues. After forty-eight hours of ligation the same extensive necrotizing and exudative process was present; and in addition, occasional fibroblasts were seen extending out from the adventitia of the blood vessels adjacent to the necrotic muscle fibers. Four days after ligation the connective tissue proliferation was more extensive; masses of necrotic muscle fibers were now surrounded by fibroblasts. From this period on, the reparative process became dominant, and at the end of a month the infarcted zone was completely replaced by a dense fibrous tissue scar, which was infiltrated with small mononuclear cells and large phagocytic cells containing golden brown pigment.

The histological changes observed here were similar to those described in detail by Karsner and Dwyer<sup>6</sup> in their studies of experimental infarction of the myocardium in dogs.

*Ligation of Coronary Vessels With Subsequent Release of Ligatures.*—In these experiments the coronary vessels were ligated for varying periods up to eight hours; the ligatures were then released and two hours later tissues were removed from the myocardium for chemical and anatomical study.

In all instances except one, the lactic acid content of the muscle from the zone supplied by the previously ligated vessels was slightly but not appreciably lower than that of the muscle from the control zone. In the one exception, Dog 59, the anterior descending branch of the left coronary artery was found occluded at autopsy by a freshly formed thrombus (Table III). The glycogen content of the affected muscle in contrast remained decreased below that of the control zone as in the first group of experiments (Table IV).

Striking anatomical changes were noted in the myocardium supplied by the previously ligated vessels except in the instance where the vessel was tied for only one-half hour, in which case no demonstrable changes were seen. In the other hearts the myocardium supplied by the previously ligated vessels was the seat of an extensive hemorrhagic infarct

which extended throughout the entire thickness of the wall, involving intensely the inner half and also the anterior one-third of the inter-ventricular septum (Table V).

TABLE III

LACTIC ACID CONTENT OF HEART MUSCLE TWO HOURS AFTER UNTYING LIGATED VESSELS

DOG NO.	NO. OF HR. BET. LIGATION AND UNTYING OF ARTERY	LACTIC ACID	
		AV. MG. /100 GR. OF TISSUE INVOLVED ZONE	UNINVOLVED ZONE
67	½	38.8	54.3
65	2	39.5	65.3
59	4	78.5	71.3
60	8	52.0	66.0

TABLE IV

GLYCOGEN CONTENT OF HEART MUSCLE TWO HOURS AFTER UNTYING LIGATED VESSELS

DOG NO.	NO. OF HR. BET. LIGATION AND UNTYING OF ARTERY	GLYCOGEN AS GLUCOSE	
		AV. MG. /100 GR. OF TISSUE INVOLVED ZONE	UNINVOLVED ZONE
81	2	158.5	528.5
68	8	281.0	757.5

TABLE V

ANATOMIC CHANGES IN THE MYOCARDIUM FOLLOWING LIGATION OF CORONARY VESSELS

DOG NO.	TIME LIGATED	MYOCARDIUM									
		EXUDATE		HEMORRHAGE		FAT		NECROSIS		FIBROSIS	
		EXP.	CON.	EXP.	CON.	EXP.	CON.	EXP.	CON.	EXP.	CON.
9	1 hr.	0	0	0	0	0	0	0	0	0	0
6	2 hr.	0	0	0	0	0	0	0	0	0	0
4	2½ hr.	0	0	0	0	0	0	0	0	0	0
5	4 hr.	0	0	0	0	0	0	0	0	0	0
8	7 hr.	0	0	0	0	0	0	0	0	0	0
10	7½ hr.	+	0	0	0	+	0	0	0	0	0
2	9 hr.	+	0	0	+	0	0	0	0	0	0
25	12 hr.	E*	0	+	0	+	+	±	0	0	0
22	16 hr.	E	0	0	0	++	0	0	0	0	0
29	28 hr.	+++E	0	0	0	++	+	++	0	0	0
30	30 hr.	+E	0	+	0	++	+	+	0	0	0
28	35 hr.	+E	0	+	0	+	0	+	0	0	0
16	2 days	++	0	0	+	+++	0	++	0	0	0
15	4 days	+++	0	0	0	+++	0	+++	0	early	0
34	33 days	0	0	0	0	0	0	0	0	+++	0
24	48 days	0	0	0	0	0	0	0	0	+++	0
20	72 days	0	0	0	0	0	0	0	0	+++	0
26 (con)	74 days	0	0	0	0	0	0	0	0	0	0

CIRCULATION REESTABLISHED FOR TWO HOURS

67	½ hr.	E	0	0	0	0	0	0	0	0	0
65	2 hr.	+E	0	+++	0	0	0	+	0	0	0
81	2 hr.	+E	0	+++	0	0	0	+	0	0	0
59	4 hr.	+E	0	+++	0	0	0	+	0	0	0
60	8 hr.	+E	0	+++	0	0	0	+	0	0	0
68	8 hr.	+++E	0	+++	0	0	0	+	0	0	0

\*E, edema.

## DISCUSSION

It is apparent from the data on the first group of experiments (Tables I and II) that the accumulated lactic acid in the ischemic myocardium results from the glycogen breakdown. In the normal heart excessive lactic acid formation is prevented by the large amount of oxygen furnished through an abundant blood supply, an amount much greater than that for an equal weight of skeletal muscle (Himwich and Castle<sup>7</sup>), Markwalder and Starling<sup>8</sup>). Indeed, it has been shown that the functioning heart with its circulation intact does not pour out lactic acid into the blood stream, but actually removes it from the circulating blood (Himwich,<sup>9</sup> McGinty<sup>10</sup>). McGinty has further shown that in instances where the blood supply to the myocardium of the intact heart is reduced by vasoconstriction following large doses of pitressin, a pouring out of lactic acid from the heart into the blood stream occurs. Associated with the vasoconstriction apparently, there is a marked degree of anoxia so that lactic acid forms and accumulates to such an extent that it diffuses into the circulation. In the present experiments the muscle in the zones supplied by the ligated vessels is functioning under conditions of extreme anoxia and accordingly utilizes its stored glycogen; with the lack of circulation in the part, lactic acid accumulates. Similar chemical changes in the affected myocardium following experimental ligation of the coronary artery in dogs have been reported by Pomodoro<sup>11</sup> and Himwich and his associates.<sup>12</sup>

In the second group of experiments in which the ligatures were subsequently removed, the lactic acid content of the myocardium in the involved zone fell below that of the control zone. Apparently, the accumulated lactic acid was washed out by the reestablishment of blood flow. That this drop was not due to a resynthesis of the lactic acid to glycogen is evidenced by the fact that the latter remained at the same low level as in the first group in which the circulation was not restored.

The absence of any demonstrable anatomical changes in the muscle tissue until eight hours after ligation was in striking contrast to the findings when the circulation was restored by the removal of the ligatures. Under the latter condition extensive hemorrhage, edema, and polymorphonuclear leucocytic exudate was present throughout the involved zones, even when the interval of ligation was only two hours. This exudative reaction indicates at least that alteration of the capillary walls has taken place. The failure of glycogen resynthesis following reestablishment of the circulation suggests that injury to the myocardial fibers themselves also may have occurred even though this was not histologically demonstrated. The lack of early exudative changes when the circulation has not been reestablished may be attributable to the absence of blood flow through the part.

## SUMMARY

1. Occlusion of the left anterior descending coronary artery and accompanying veins results in an increase of the lactic acid and a decrease of glycogen content of the muscle deprived of its circulation.

2. When the circulation is reestablished for two hours by release of the ligatures after varying intervals of occlusion, the lactic acid content of the affected muscle returns to normal, but restoration of the glycogen content does not occur.

3. When the circulation is restored in the myocardium by release of the ligature, a series of changes is observed histologically that contrast with the usual picture of experimental infarction.

These experiments were planned and carried out during 1932-1934 under the direction of Dr. Raymond Hussey.

## REFERENCES

1. Sutherland, F. A., and Dial, D.: *Proc. Soc. Exper. Biol. & Med.* 33: 1430, 1933.
2. Grayzel, D. M., Tennant, R., Stringer, S., Sutherland, F. A.: *Preliminary Report, Proc. Soc. Exper. Biol. & Med.* 31: 837, 1934.
3. Harris, B. R., Sutherland, F. A., Ramsey, E. M., and Gaiser, D. W.: *Proc. Soc. Exper. Biol. & Med.* 31: 222, 1933.
4. Friedemann, T. E., and Graeser, J. B.: *J. Biol. Chem.* 100: 291, 1933.
5. Yannet, H., and Darrow, D. C.: *J. Clin. Investigation* 12: 779, 1933.
6. Karsner, H. T., and Dwyer, J. E.: *J. M. Research* 34: 21, 1916.
7. Himwich, H. E., and Castle, W. B.: *Am. J. Physiol.* 83: 92, 1927.
8. Markwalder, J., and Starling, E. H.: *J. Physiol.* 47: 275, 1913-1914.
9. Himwich, H. E.: *Yale M. J.* 4: 259, 1932.
10. McGinty, D. A.: *Am. J. Physiol.* 98: 244, 1931.
11. Pomodoro, I. G.: *Fisiol. e med.* 4: 401, 1933.
12. Himwich, H. E., Goldfarb, W., and Nahum, L. H.: *Am. J. Physiol.* 109: 403, 1934.

## A STUDY OF THE VARIATIONS OF THE RS-T SEGMENT IN EXPERIMENTAL VENTRICULAR TRAUMA\*

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ALTHOUGH considerable evidence has been presented concerning the significance and classification of the RS-T changes associated with cardiac infarction, no attempt has been made to explain or to evaluate the mechanisms responsible for the production of these characteristic electrocardiographic alterations when specific areas of the heart are injured. Subsequent to Parkinson and Bedford's presentation<sup>1</sup> of their classification of T<sub>1</sub> and T<sub>2</sub> types of curves, most of the experimental and clinical work on this subject has been utilized to obtain a purely arbitrary correlation of the location of infarcts with the electrocardiographic variations (see Barnes<sup>2</sup> for review). The evidence on this point has been conflicting; some of the workers, in fact, consider the conclusions evolved therefrom to be based merely upon fortuitous findings.<sup>3, 4</sup>

While much work has been done on the relationship of the direction of the main deflection of the extrasystolic curve to the point of stimulation in the ventricles, more specific data were presented in a recent paper by Abramson and Weinstein.<sup>5</sup> They noted that the direction of the initial complex of experimental ventricular extrasystoles, recorded with the three standard leads, depended upon the relative position of the point of stimulation in the mass of ventricular muscle and upon the particular orientation of the point and muscle mass to the recording lines of the leads. It is known that the electrical changes produced by stimulation and by injury of tissue have in common the development of negativity at the site of application (the only main differences being the magnitude and duration of the effect produced in each case). Accordingly, it was thought that possibly the same relationship that exists between the location of the point of origin of the extrasystole and the direction of its recorded main deflection might also exist between the site of myocardial trauma and the resulting characteristic electrocardiographic variations. Therefore, this study was undertaken to compare electrocardiographic effects of stimulation of various portions of the cat's ventricles with those of cauterization of the same areas. In this way it was hoped some light might be cast on the fundamental factors responsible for the form and type of RS-T changes, and on how they are influenced by the anatomical location of the injured area.

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## METHOD

The experiments reported below were performed on thirteen cats under dial anesthesia, injected intraperitoneally. Artificial respiration was instituted, the heart exposed by making a U-shaped flap of the anterior chest wall, and then the pericardium was slit. Control electrocardiograms, using the three standard leads, were recorded before and after these operative procedures. After numerous trials, it was found that the most constant results were obtained by studying the following six sites (Fig. 1): (1) Anterior surface of the right ventricle; (2) anterior aspect of the interventricular septum with the boundaries extending onto both ventricles; (3) left ventricle anteriorly at the base; (4) left ventricle anteriorly at the apex; (5) left ventricle posteriorly; (6) right ventricle posteriorly.

The ventricles were stimulated by means of an electrode composed of two fine steel wires, encased in a bent glass tube and insulated with sealing wax. The electrode was connected to the binding posts of the secondary coil of an inductorium, and the primary circuit was broken at a rate slightly above the sinus beat by means of a Harvard spring interrupter. Records of extrasystoles were obtained from each of the selected areas, special attention being paid to the one region subse-

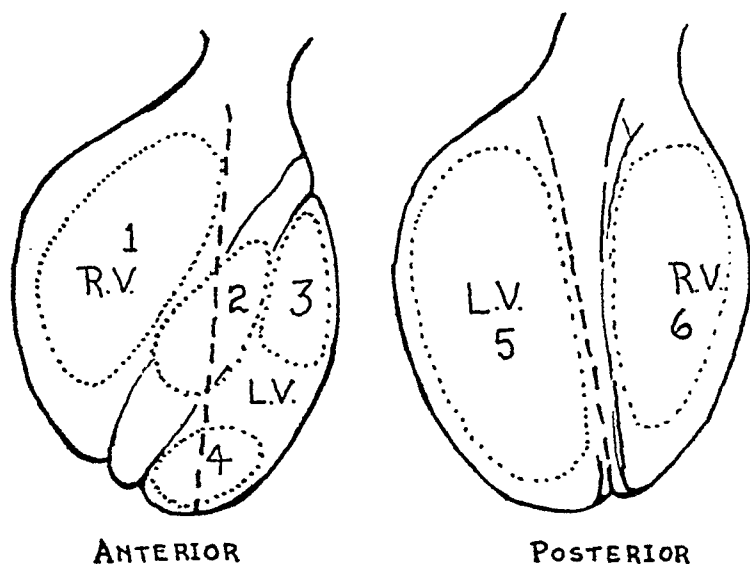


Fig. 1.—Schematic drawings of anterior and posterior surfaces of the ventricle. The six areas enclosed by the dotted lines represent the ones studied: 1, right ventricle anteriorly; 2, anterior aspect of interventricular septum; 3, basal portion of left ventricle anteriorly; 4, apical portion of left ventricle anteriorly; 5, posterior surface of left ventricle; 6, posterior surface of right ventricle. The broken lines on both drawings represent the line of transition for Lead I.

quently to be cauterized. In the case of the latter, stimuli were applied to a number of additional points at the periphery and in the center of this site. An area of injury was produced in this previously outlined site by means of an electric cauter, following the procedure of Crawford and his associates.<sup>6</sup> The size of the injury was generally about 1.5 cm. in diameter and extended for about a millimeter into the myocardium. In all instances, care was taken to limit the cauterization to that part of the heart under study at the moment. Electrocardiograms were obtained immediately after the injury, first with the normal sinus rhythm, and then with a repetition of stimulation of all six of the designated areas. Following the production of the extrasystoles, a control record was again obtained to make certain that the RS-T alteration produced by the cauterization was still present. In a number of experiments, after the electrocardiographic effects consequent to cauterization had entirely disappeared, a second area was studied. At times, when the site of injury was located on the anterior surface of the heart, it was found necessary, in order to bring out more clearly the resulting electrocar-



diographic alterations, to apply a pad of cotton dipped in warm saline to the anterior surface of the heart and to cover this with the chest flap. This difference in technic required in the case of the anterior heart surface may be attributed to the reduction in conductivity of the action currents from the heart due to the removal of the anterior chest wall (in contrast to the posterior surface which retains essentially its normal relationship to the surrounding tissues). Wood and Wolferth<sup>7</sup> found a similar difficulty in obtaining electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery, unless they worked with very little of the heart exposed.

In order to test the effect of rotation of the heart on the curve produced by injury at a particular point, the following procedure was carried out in certain experiments: Stay sutures were sewed into the epicardium of the ventricles, one at the apex of the heart and one at each lateral surface. By means of these, the heart was made to rotate to the right or left on its long axis, and electrocardiograms obtained in each position and finally after return to the normal position. Control electrocardiograms were taken in some cases with the heart displaced as described but without any injury by cauterization. The effect on the RS-T interval in these controls was, for the most part, negligible.

Generally the tension of the string was such that the introduction of 1 mv produced a deflection of 1.5 cm., except when the extrasystolic waves were recorded, in which case the usual relationship of 1 mv to 1 cm. deflection existed.

### RESULTS

For the sake of convenience in recording, the electrocardiographic findings obtained with artificial stimulation and with cauterization are incorporated in Table I, and only explanatory notes and a summation of

TABLE I  
EFFECT OF STIMULATION AND SUBSEQUENT CAUTERIZATION OF SITES ON THE EPICARDIAL SURFACE OF BOTH VENTRICLES

SITE STUDIED	CAT NO.	DIRECTION OF INITIAL DEFLECTION OF EXTRA-SYSTOLIC WAVE			DIRECTION OF RS-T SEGMENT SUBSEQUENT TO CAUTERIZATION		
		LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
Right ventricle anteriorly	4	+	+	+	0	-	-
	8	+	+	+	0	=	=
	7	+	+	+	-	-	-
Anterior surface over septum	6	±	+	+	+	=	=
	12	±	+	+	+	=	=
Left ventricle anteriorly at base	11	+	+	+	+	=	=
	15	-	+	+	+	-	-
	16	-	+	+	+	=	=
Left ventricle anteriorly at apex	3A	-	-	-	+	+	0
	14	±	-	-	+	++	++
	13A	-	-	-	-	++	++
Left ventricle posterior surface	2	-	-	-	+	+	+
	3B	-	-	-	+	+	+
	5A	-	-	-	+	++	++
	9	-	-	-	+	++	++
Right ventricle posterior surface	13B	-	-	-	0	++	++
	1	+	-	-	0	+	+
	5B	+	-	-	-	++	++
	10	+	-	-	-	++	++

+ Indicates a positive deflection.

- Indicates a negative deflection.

The number of these indicates grossly the relative amplitude of the waves.

0 Represents no change in RS-T segment following cauterization.

results are given herewith. The presentation of the data is limited to listing, first, the direction of the initial deflection of the extrasystolic wave obtained from stimulation of a specific area and, second, the direction of the deviation of the RS-T segment with normal sinus rhythm, following cauterization in the same site. In the instances in which the direction of the initial deflection of the extrasystolic complexes obtained from the center and from the periphery of the site under study varied, the one selected for tabulation represents the most common and characteristic finding.

In the case of Lead I, it was noted that generally, with normal sinus rhythm, the amplitude of the waves was small, so that the effect of cauterization on the RS-T segment in some instances was insignificant.

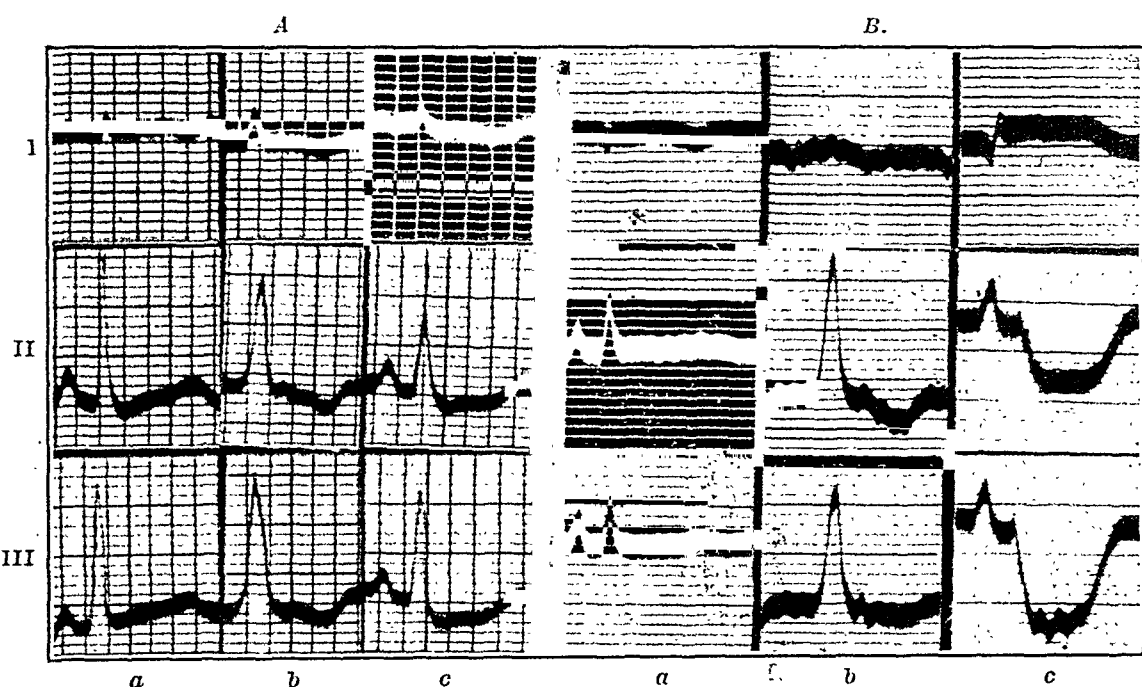


Fig. 2.—A, Experiment 16, anterior surface of right ventricle: *a*, control with normal sinus rhythm; *b*, extrasystolic waves obtained upon stimulation of this site. Initial deflection upright in all three leads. *c*, curves obtained with normal sinus rhythm after cauterization in the same area. Depression of RS-T in all three leads.

B, Experiment 6, anterior surface of septum including contiguous portions of both ventricles: *a*, control with normal sinus rhythm; *b*, extrasystolic waves obtained by stimulation at this site. Initial deflection in Lead I almost isoelectric and in the other two leads upright. *c*, curves obtained with normal sinus rhythm after cauterization in the same area. Elevation of RS-T in Lead I and depression in the other two.

Time,  $\frac{1}{25}$  second; 1 mv = 1.5 cm. for curves obtained with sinus rhythm. 1 mv = 1 cm. for curves obtained by artificial stimulation.

On the other hand, the changes in Leads II and III were consistently marked, in some cases being of such magnitude as to hide the R- and T-waves completely.

*Comparison of the Direction of the RS-T Alterations With the Direction of the Main Deflections of the Extrasystolic Waves.*—From an examination of Table I it will be seen that in Lead I the direction of the RS-T segment following cauterization appears to depend upon whether the damage was situated grossly on the right or the left ventricle, i.e.,

the direction of the RS-T segment was consistently negative in instances of cauterization on the right ventricle (Figs. 2A and 4A) and positive in instances of cauterization of the left ventricle (Figs. 3A and B and 4B). The only exceptions were the four cases in which no change was observed (Experiments 1, 4, 8, and 13B) and the one case (Experiment 13A) in which injury to the left ventricle anteriorly at the apex produced an RS-T depression. In those experiments in which the trauma extended onto both ventricles (Experiments 6 and 12) the direction of the RS-T segment was similar to that obtained on the left ventricle (Fig. 2B).

The changes in Leads I and II were generally alike. In all instances of cauterization on the anterior surface of the heart (except the left ventricle at the apex) the RS-T segment was depressed in both leads

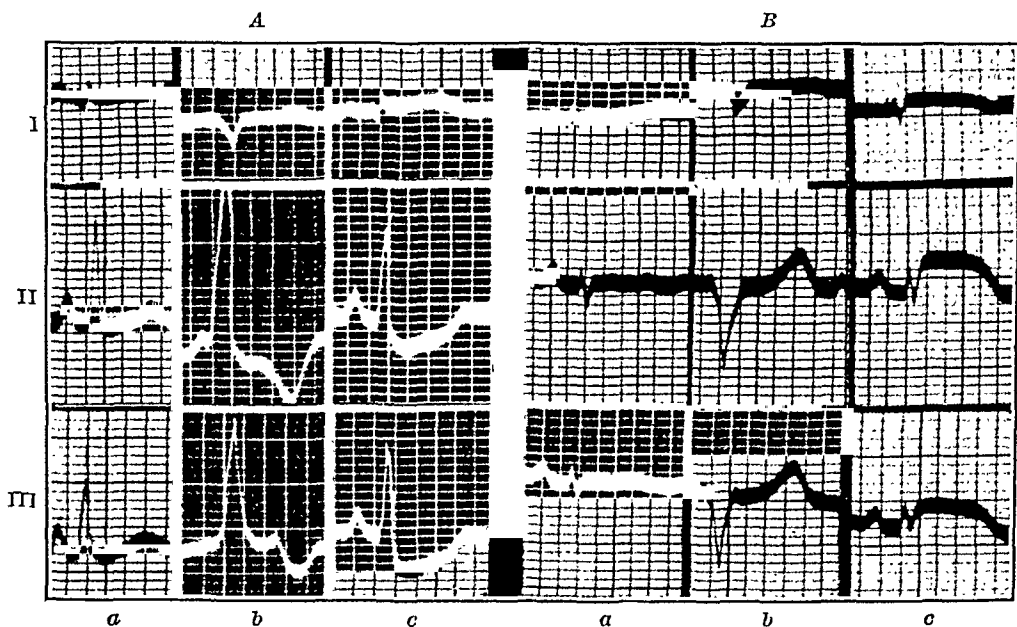


Fig. 3.—A, Experiment 15, left ventricle anteriorly at the base; a, control; b, extrasystolic waves obtained by stimulation of this site. Main deflection negative for Lead I and positive for the other two leads. c, curves with normal sinus rhythm after cauterization in the same area. Elevation of RS-T in Lead I and depression in the other two leads.

B, Experiment 14, left ventricle anteriorly at the apex: a, control; b, extrasystolic waves obtained by stimulation of this site. Main deflection negative in all three leads. c, curves with normal sinus rhythm after cauterization in the same area. Elevation of RS-T in all three leads.

(Figs. 2A, 2B, and 3A). For the entire posterior surface of the heart, either right or left ventricle, as well as for the left ventricle anteriorly at the apex, the direction of the RS-T segment was consistently positive in both leads (Figs. 3B, 4A, and 4B).

In reference to the direction of the initial deflection of extrasystolic waves, the results were essentially similar to those obtained by Abramson and Weinstein. In Lead I the initial complex was upwardly directed for points of stimulation to the right of the lines of transition on both surfaces (Figs. 2A and 4A), and downwardly directed for com-

parable areas to the left of it (Figs. 3A, 3B, and 4B). These lines of transition for Lead I grossly followed the location and direction of the interventricular grooves on both surfaces except that the anterior one in its upper portion extended somewhat on to the right ventricle, and in its lower third obliquely onto the apex of the left ventricle\* (Fig. 1).

The types of extrasystolic waves obtained in Leads II and III were alike grossly; the initial deflection was positive in cases of stimulation of points on the anterior surface of the heart (Figs. 2A, 2B, and 3A), except for the inferior portion of the left ventricle anteriorly. From the latter region and from the entire posterior surface of both the right and left ventricles, the main initial deflection in Leads II and III was downwardly directed (Figs. 3B, 4A, and 4B).

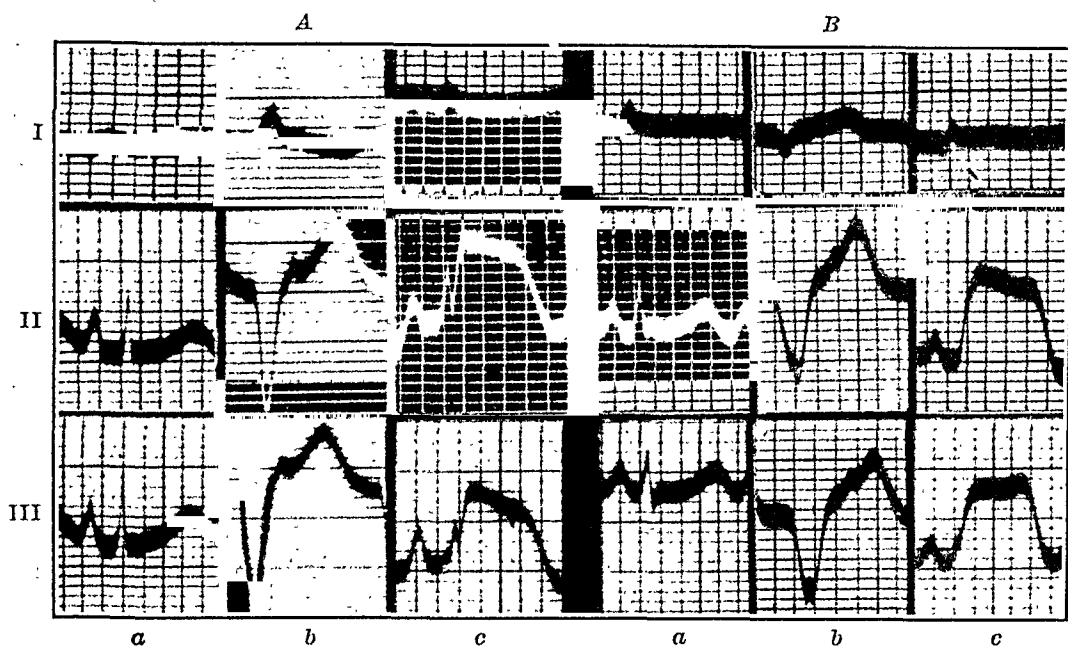


Fig. 4.—A, Experiment 10, right ventricle posteriorly: *a*, control; *b*, extrasystolic waves obtained by stimulation of this site. Main deflection positive for Lead I and negative for the other two leads. *c*, curves with normal sinus rhythm after cauterization in the same site. Slight depression of RS-T in Lead I and marked elevation in the other two leads.

B, Experiment 9, left ventricle posteriorly: *a*, control; *b*, extrasystolic waves obtained by stimulation of this site. Main deflection negative for all three leads. *c*, curves with normal sinus rhythm after cauterization in the same site. Slight elevation of RS-T segment in Lead I and marked elevations in the other two leads.

It is therefore apparent from the above that the same factors which affect the direction of the initial deflection of extrasystolic waves also influence the direction of the displacement of the RS-T interval following cauterization. Moreover, in all instances, cauterization of an area from which extrasystolic waves had previously been elicited resulted in an RS-T change which was consistently opposite in phase to the chief initial deflection of the extrasystole. (Figs. 2, 3, and 4.) Such

\*This may explain why in an experiment (Experiment 13A) in which the apex of the left ventricle, anteriorly, was cauterized, a right ventricular effect was recorded, i.e., an RS-T depression in Lead I. The damage probably extended somewhat to the right of the line of transition.

constancy of results would appear to place these findings beyond the realms of mere coincidence. This relationship between portions of curves apparently having no common denominator will be given significance in a later paper in which the theoretical basis for the observed changes will be discussed.<sup>8</sup>

*Effect of Rotation of the Heart upon the RS-T Alteration.*—It has been shown<sup>5</sup> that stimulation of the right side of the ventricular mass results in an upward chief initial deflection in Lead I. This is so whether the right side of the ventricular mass, as in the normally placed heart, is predominantly right ventricle or whether the heart is so rotated that the left ventricle becomes the right side of the ventricular mass and it then receives the stimulus.

In order to determine whether an alteration in the position of the site of cauterization relative to the recording lead lines also produces a change in the type of RS-T deflection, and whether a correlation exists comparable to that obtained with extrasystoles,<sup>5</sup> the heart was rotated on its long axis immediately after injury, in a number of experiments. By means of stay sutures it was turned either to the right, so that a

TABLE II

EFFECT OF ROTATION OF HEART ON THE RS-T ALTERATION SUBSEQUENT TO CAUTERIZATION

SITE OF LESION	CAT NO.	ORIGINAL RS-T SEGMENT			NEW SITE OF LESION	SUBSEQUENT RS-T SEGMENT		
		LEAD I	LEAD II	LEAD III		LEAD I	LEAD II	LEAD III
<i>Rotation to the Right So as to Expose More of the Left Ventricle Anteriorly</i>								
Right ventricle anteriorly	16	-	-	-	Posteriorly and on right side	-	+	+
Anterior surface of septum	12	+	=	=	Posteriorly and to the right	-	++	++
Left ventricle anteriorly	15	+	-	-	Laterally and to the right	-	-	0
Left ventricle posteriorly	2	++	++	++	Anteriorly and to the left	++	=	=
Right ventricle posteriorly	10	-	++	++	Anteriorly and to the left	+	0	-
<i>Rotation to the Left So That Anterior Surface of Heart Is Made Up Entirely of Right Ventricle</i>								
Anterior surface of septum	12	+	-	-	Laterally and to the left	+	0	-
Left ventricle anteriorly	15	+	-	-	Posteriorly and to the left	+	+	0
Right ventricle anteriorly	16	-	-	-	Laterally and to the left	+	-	-
Left ventricle posteriorly	5	0	+	+	Posteriorly and to the right	0	+	+
Right ventricle posteriorly	10	-	++	++	Anteriorly and to the left	++	=	=

+ Indicates a positive direction.

— Indicates a negative direction.

The number of these indicates grossly the relative magnitude of RS-T change.

0 Represents no RS-T alteration.

greater part of the left ventricle presented anteriorly, or to the left so that the entire anterior surface of the heart was made up of right ventricle. It will be noted from Table II that, when the position of the injury was changed by these manipulations from a posterior to an anterior position, or vice versa, the direction of the RS-T deflection in Leads II and III became reversed (Fig. 5A and B). For example, if a heart in which the anterior surface of the intraventricular septum had been cauterized, resulting in a depression of the RS-T segment in Leads II and III, was now rotated so that the injured portion was situated posteriorly, a definite elevation of the RS-T segment in these leads was noticed (Fig. 5B). If the position of the heart was so changed that trauma to the left of the hypothetical line of demarcation for Lead I was changed to the right of it, or vice versa, a definite reversal in the

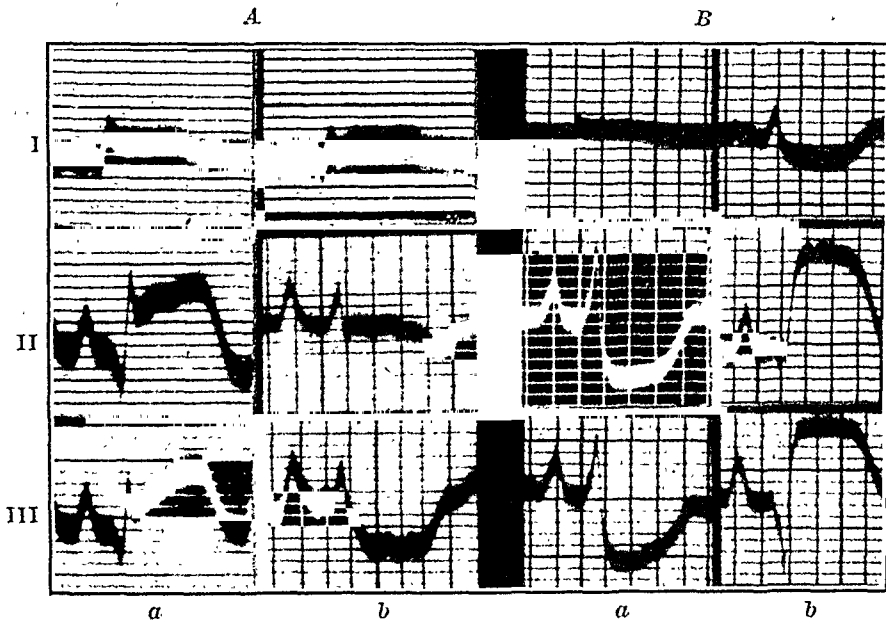


Fig. 5.—Effect of rotation of the heart upon the direction of the RS-T segment. All curves obtained with normal sinus rhythm.

A, Experiment 2, *a*, after cauterization of the posterior surface of the left ventricle. Elevation of the RS-T segment in all three leads. *b*, after rotation of the heart to the right so as to place the burn anteriorly but still on the left. RS-T still elevated in Lead I, isoelectric in Lead II, and definitely depressed in Lead III.

B, Experiment 12, *a*, after cauterization of anterior surface to interventricular septum. RS-T elevated in Lead I and markedly depressed in the other two leads. *b*, after rotation of the heart far enough to the right so as to place the burn posteriorly and to the right. Depression of RS-T in Lead I and elevation in Lead II and Lead III.

direction of the RS-T segment in this lead took place. Thus, trauma on the left ventricle anteriorly, producing an RS-T elevation in Lead I caused an RS-T depression when the damaged area was rotated to the right side. The results of the rotation experiments are further evidence for the view that the alteration in the direction of the RS-T segment is dependent upon the relationship of the site of injury to the entire ventricular mass and to the recording lead lines and not upon any relationship to anatomical landmarks in the heart itself.

*Effect of Prior Cauterization on the Contour of the Extrasystolic Waves.*—Comparisons of the curves obtained by stimulation of the six designated areas before and after cauterization revealed that a change in the contour of the second series was present, evidently as a result of the injury. This alteration consisted of either an elevation or a depression of the usually very short isoelectric interval existing between the initial and terminal deflections (Fig. 6). At times the degree of deviation was of sufficient magnitude to obliterate completely or reverse the direction of the terminal and even the initial phase of the extrasystolic wave. It was found, moreover, that for any specific area of cauterization, the direction of this change in the extrasystolic wave was consistently in the same phase in the same lead, no matter where on the heart surface the stimuli were subsequently applied. Further, the direction

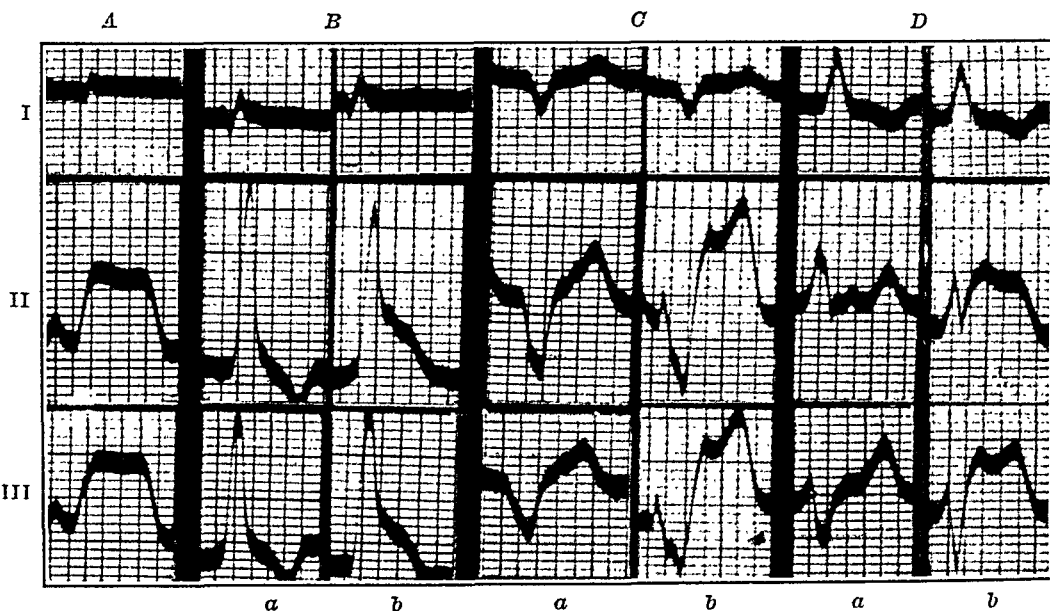


Fig. 6.—Extrasystolic curves subsequent to cauterization.

A, Experiment 9, normal sinus rhythm following cauterization of the left ventricle posteriorly. Very slight elevation in Lead I, marked elevation in other two leads.

B, extrasystolic waves obtained from stimulation of anterior surface of right ventricle: a, before cauterization; b, after cauterization.

C, extrasystolic waves obtained from stimulation of left ventricle posteriorly: a, before cauterization; b, after cauterization.

D, extrasystolic waves obtained from stimulation of the right ventricle posteriorly: a, before cauterization; b, after cauterization. An elevation of the short interval, normally isoelectric, is observed in all the extrasystolic waves of Leads II and III after cauterization. This elevation is similar in direction to the RS-T alteration observed in the control records with sinus rhythm, A. Comparable results in Lead I are not discernible.

of the change in the three leads coincided with the RS-T change obtained with normal sinus rhythm. For example, if the left ventricle was cauterized posteriorly, the change in the standard leads consisted of an elevation of the RS-T segment in all three leads (Fig. 6A). If now, extrasystoles were elicited although the direction of these initial deflections conformed to those anticipated from the location of the point of stimulation, the change in the isoelectric period was in a positive direc-

tion in all three leads for all sites of stimulation on both ventricles (Fig. 6B, C, and D). The only exception was the occasional absence of change in the extrasystolic waves recorded with Lead I when the original RS-T deviation in this lead was not pronounced.

#### SUMMARY

In an attempt to explain the characteristic changes observed in the RS-T segment of the standard leads with infarction of specific areas of the heart, six sites on the cat's ventricle were studied. In each experiment one of these was cauterized and the electrocardiographic effects compared with those obtained by previously *stimulating* the same site so as to produce extrasystoles. A comparison was also made between extrasystolic waves elicited from all six regions before and after cauterization of one of them.

1. It was found that the site of cauterization determined the direction of the RS-T interval displacement in the same manner as the site of stimulation determined the direction of the initial deflection of the extrasystolic complex.

2. It was also observed that the RS-T segment was consistently opposite in phase to that of the initial deflection of the extrasystolic wave obtained by stimulation of the site before cauterization.

3. Confirmatory evidence was elicited by changing the position of the trauma by rotating the heart and recording the difference in the displacement of the RS-T segment.

4. It was found that the direction of the deviation of the comparative RS-T interval in the experimental extrasystolic wave elicited after cauterization was determined by the site of the previous injury regardless of the point of stimulation producing the extrasystole.

5. It would appear that in the cat's heart subjected to cauterization: (a) in Lead I the direction of the RS-T deviation depends upon whether the trauma is situated grossly on the right or left ventricle, and

- (b) In Leads II and III, the direction of the RS-T deflection depends upon whether the site of injury is on the anterior or the posterior surface of the heart, with the exception that the anterior apical portion of the left ventricle shows the same changes in direction as the posterior surface.

#### REFERENCES

1. Parkinson, J., and Bedford, D. E.: *Heart* 14: 195, 1927-1929.
2. Barnes, A. R.: *Arch. Int. Med.* 55: 457, 1935.
3. Gilchrist, A. R., and Ritchie, W. T.: *Quart. J. Med.* 23: 273, 1930.
4. Korey, H., and Katz, L. N.: *Am. J. M. Sc.* 188: 387, 1934.
5. Abramson, D. I., and Weinstein, J.: *Am. J. Physiol.* 115: 569, 1936.
6. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: *AM. HEART J.* 7: 627, 1932.
7. Wood, F. C., and Wolferth, C. C.: *Arch. Int. Med.* 51: 771, 1933.
8. Fenichel, N., Shookhoff, C., and Abramson, D. I.: *AM. HEART J.* (In press.)
9. Wilson, F. N., Macleod, A. G., and Barker, P. S.: *AM. HEART J.* 6: 637, 1931.



LIGATION OF THE CORONARY ARTERIES IN JAVANESE  
MONKEYS\*†

### III. FURTHER THEORETICAL CONSIDERATIONS OF THE CHANGES IN THE VENTRICULAR ELECTROCARDIOGRAM, WITH ILLUSTRATIVE EXPERIMENTS

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AS THE most prominent and most acute electrocardiographic symptom following coronary ligation in monkeys (*Macaca*) we described in Parts I and II of this paper,<sup>1</sup> a deviation of the S-T segment which showed in each animal a very definite direction. The direction of the so-called electrical S-T-axis was calculated or constructed by the application of the principles of the equilateral triangle, and it proved to point

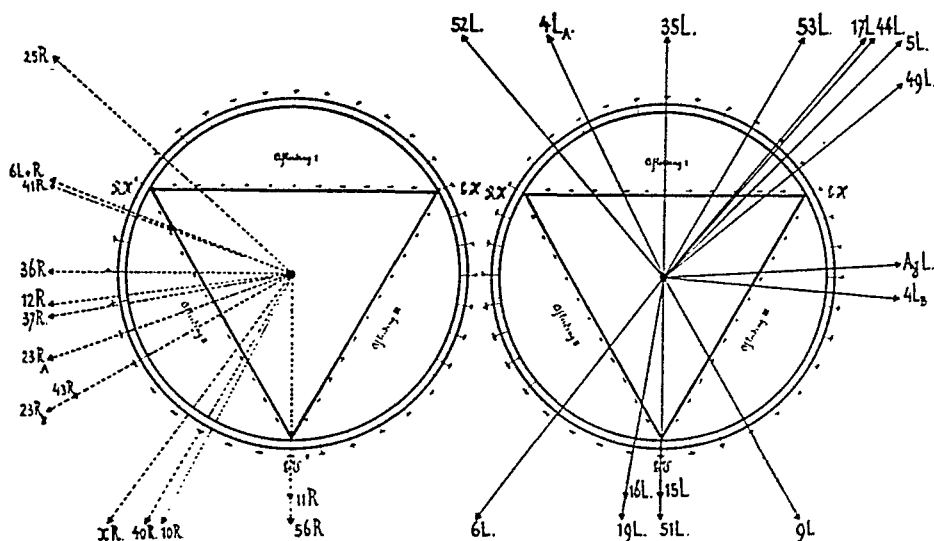


Fig. 1.—Direction of the electrical S-T axis as found in different monkeys after ligation of right coronary artery (R) and anterior descending branch of left coronary artery (L).

preponderatingly in the direction of that part of the heart most affected by the circulation disturbances, as was shown before and is reproduced here in Fig. 1.

In order to get a further insight into the acute results of ligations on the functional conditions of the monkey heart, special investigations were made: in the first place, on the problem whether, as a rule, after coronary ligation acute dynamic changes in the action of the heart *as a whole* were to be found.

In general, such changes were not observed, a finding which agrees with various comparable reports in the literature, for instance those of

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†Preliminary communication on portions of the subject-matter of this paper was made to the 7th Science Congress at Batavia, Java, on October 25, 1935.

Feil and his coworkers,<sup>2</sup> who after ligating the anterior descending branch in dogs found "surprisingly small changes in the mean blood pressure"; and of Orias,<sup>3</sup> who also in dogs sometimes even found the heart action after four minutes dynamically somewhat better than normal and concludes that compensatory mechanisms, especially in the undamaged heart muscle parts, very promptly come into play.

Figure 2 shows one of our experiments in this direction.

In a *Macaca irus* before, during, and after ligation (L) of the anterior descending branch, records were made of respiration and blood pressure, the latter traced from the carotid with an elastic manometer. The changes to be observed in the respiration, systolic and diastolic blood pressure, and pulse amplitude, both in size and frequency, are very slight indeed and even after a considerable time, as also other observations showed us, are usually practically absent, unless, as in Fig. 2, ventricular fibrillation sets in. But even just before this fibrillation, which was preceded by two extrasystoles, there were no definite changes in the functions in question. We are certain that here quite definite S-T deviations had already developed as they were never absent at that stage after left ligation.

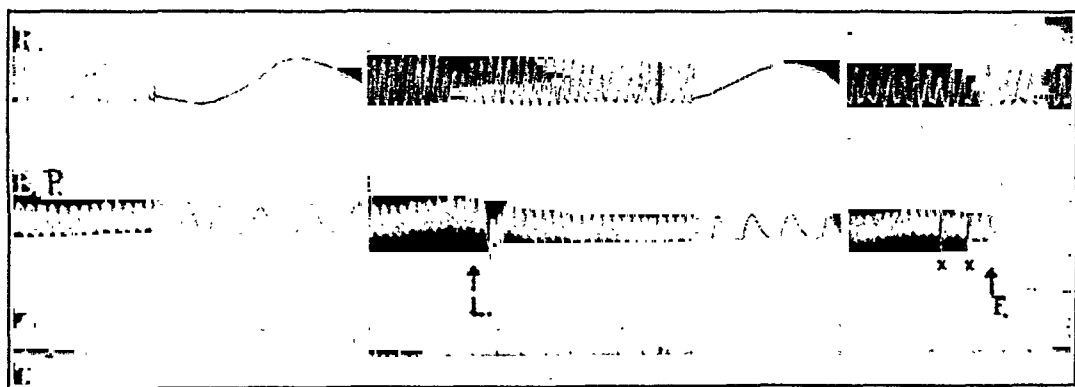


Fig. 2.—Registration of respiration (R) and arterial blood pressure (B.P.) in a monkey, during ligation of the ramus descendens anterior.

Part 1: Before operation. Part 2: Just before and after ligation (L). Part 3: About 10 min. after ligation, extrasystoles (X) and fibrillation (P). Z, zero line of elastic manometer. T, time in 5 sec. On the last of Parts 1 and 2 the rate of drum movement was quickened.

As has been said before, in the great majority of our electrocardiograms the heart rate, which can be considered as a very sensitive indicator for possible postoperative disturbances in the dynamic functions of the heart as a whole, did not show any definite changes in our monkeys after ligation.

Since, as has been mentioned, the changes in the ventricular electrocardiogram, namely the S-T deviations, begin so quickly that it is possible even during the course of the experiment to predict from the change in string movements whether the ligation has or has not been successful, we are of the opinion that these electrical phenomena are independent of any definite hypofunction or hyperfunction of the heart as a whole. In this we agree with Orias<sup>3</sup> and with Wood and Wolferth.<sup>4</sup> At any rate, the disturbance in the dynamics of the heart, if it is present at all

in the heart *locally*, is so slight that it is not shown by the methods used in Fig. 2 for investigating blood pressure and respiration.

For the purpose of learning more about the changes in the heart muscle function under the influence of muscular asphyxia, experiments on the whole animal are less suitable, among other reasons because of the vagus effects and the peripheral vascular reactions caused by a general anoxemia.<sup>5</sup>

In our opinion, however, the isolated heart may quite properly be regarded as an example of a many times enlarged heart element. According to Wiggers,<sup>6</sup> the total action of the heart may be considered as being a rapid summation of successive contractions of the individual fractions of the organ, and any change in the total action, if it results from a factor which affects all the parts alike, may be regarded as evidence of similar alterations in the fractionate (ultimate) contraction curves, as long as the ventricles are being excited along the normal pathways.

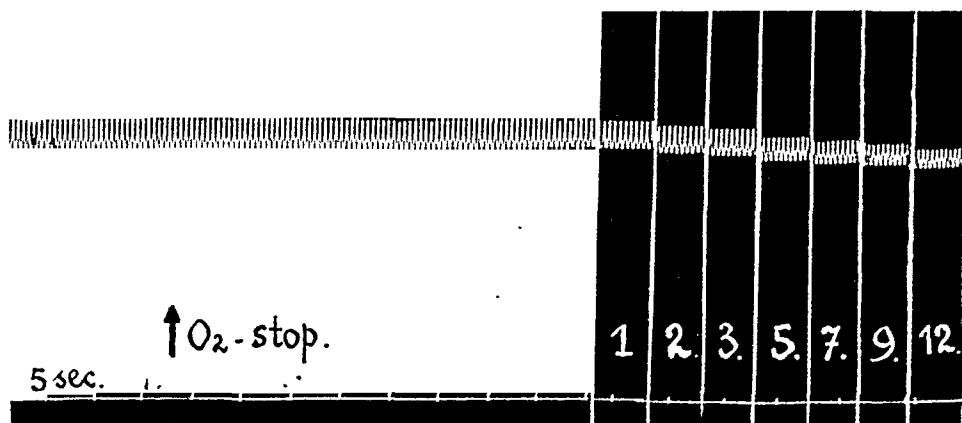


Fig. 3.—Mechanogram of excised Macaca heart perfused with Ringer-Locke (Langendorff method). At ↑ oxygenated saline is replaced by the nonoxygenated solution. Number of next segments shows number of minutes after stoppage of oxygenated saline.

In the literature regarding the relation between oxygen and muscle function, respectively heart function, the monkey heart is not discussed.<sup>7-10</sup> We therefore attempted to get some further information by causing changes in the circulation in monkey hearts isolated and perfused by the method of Langendorff and by observing what changes in the contraction curves accompanied them. These changes may then be considered as reproducing on a large scale, but accurately, the changes that occur in the fractionate contraction curve of each separate heart unit, the oxygen supply of which is disturbed.

In these experiments, which were performed in our laboratory at an average room temperature of 30° C. (86° F.), special care was taken to keep the temperature of the heart as constant as possible.

Two observations are described here as typical of many.

A Macaca heart (see Fig. 3) was perfused according to the method of Langendorff with oxygenated Ringer-Locke solution. When we switched over to nonoxygenated Ringer-Locke solution the ventricular contractions continued for about three minutes practically unchanged. Thereafter the heart action gradually died away. We did not observe a temporary increase in amplitude or any changes in frequency. A slight fall in the base of the curve indicated that there was probably a slight reduction of muscle tonus.

The circulatory changes in the experiment described above are not entirely comparable with those present after coronary ligation, because, although the supply of oxygen was reduced, any accumulation of the waste products of metabolism was combated by the continual perfusion. In order to secure this accumulation of metabolites in addition to the deficiency of oxygen special experiments, one of which will be described (illustrated by Fig. 4), were then made.

In a Macaca heart which was perfused according to the method of Langendorff with oxygenated Ringer-Locke solution, after the amplitudes of the heart contractions had become constant, the entire perfusion was stopped. Directly thereafter, during

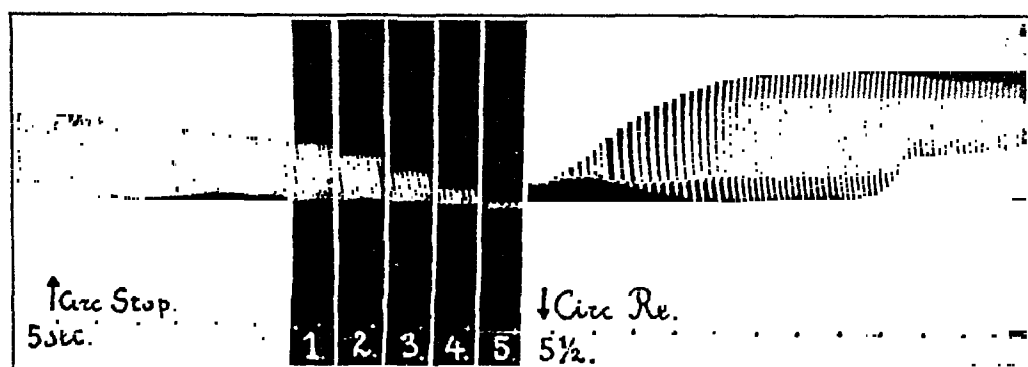


Fig. 4.—Mechanogram of excised Macaca heart, perfused with oxygenated Ringer-Locke solution. At  $\uparrow$  whole circulation is stopped. Hyperactive phase during  $\pm 12$  seconds, followed by progressive decrease in amplitude of movements. Next segments: after 5 min. heart movements nearly stopping; after  $5\frac{1}{2}$  min. restoration of circulation (Circ. Re.) followed by hyperactive phase of  $\pm 40$  sec.

a period of about 12 sec., a phase developed in which the tonus of the left ventricle decreased, but the size of the contractions temporarily increased, only to fall off gradually again. The original amplitude was 18 mm.; the circulation being stopped, it became after 5 sec. 21 mm., after about 12 sec. again 18 mm., after 1 min. 15 mm., after 2 min. 12 mm., after 3 min. 8 mm., after 4 min. 4 mm., after 5 min. 2 mm. After  $5\frac{1}{2}$  minutes, the heart movements just having stopped, circulation was restored. The heart recovered, passing again through a hyperactive phase, this time lasting about 40 seconds.

In this last experiment, therefore, in which the accumulation of the metabolites occurred to a higher degree, we observed a temporary mechanical hyperfunction (staircase) during the first period in which they were being piled up, which was followed, however, within 12 seconds by a gradually increasing hypofunction.

It is possible that this temporary hyperfunction, the existence of which has been described in the skeletal muscles of birds in similar circumstances by Van Dyk,<sup>11</sup> might, if the coronary circulation is locally dis-

turbed, sometimes last longer in the heart part involved, but we did not get that impression. It is true that Rothberger<sup>12</sup> mentions that, after tying off very small branches of the anterior descending artery, the heart contractions occasionally became more powerful, but, even so, only for a very short period. We, as well as he and others,<sup>3, 12-16</sup> in examining the portion of the heart concerned after ligation, have usually observed decrease of activity in addition to discoloration.

The principal point is, however, that while accepting these *local* reductions of activity, possibly preceded by a brief *local* increase of function, as facts, we deny that there would be any right because of them to speak of a hyperfunction or hypofunction of the left or right heart *as a whole*. As a rule, as has been said above, the latter could not be observed in the great majority of our cases. Also clinical symptoms of heart failure appeared in only a few of our cases.

A local hyperfunction is, then, either absent entirely or of too short duration to explain the S-T deviation.

It would therefore be possible to consider a local hypofunction in the sense of a decrease of a local action current as the cause of the deviation. An argument against this, however, is the fact that the S-T deviations begin to fade away in an average time of one hour and often finally completely disappear. It is not at all probable that a local hypofunction would so quickly diminish, since the locally disturbed circulation is not restored soon enough, as appears from the formation of an infarct (compare also Orias<sup>3</sup>).

The fact, observed by us and others,<sup>17</sup> that the development of the S-T deviation is usually not accompanied by a change in the still visible part of the QRS complex, nor, according to our measurements, by a prolongation of ventricular systole, makes it hardly probable that the phenomenon could depend on depressed conduction.<sup>18</sup>

Could it be possible that the S-T deviation might be an electrical phenomenon caused by a systolic stretching of the inactive or less active parts of the heart? Such a stretching has been observed after coronary ligation by Lewis<sup>13</sup> in dogs and by us sometimes in monkeys and has also been described recently by Tennant and Wiggers.<sup>19</sup> Stretched tissues may yield deformation currents (de Meyer<sup>20</sup>). Is then the deviation after ligation the result of the interference of the ventricular electrocardiogram with a systolic deformation current?

We believe this to be improbable for the following reasons:

First, such deformation currents are too small (Gilson<sup>21</sup>) to be able to cause the S-T deviations, which are often of considerable size. Second, one may conclude from the curves of de Boer<sup>22</sup> that, at least in the frog heart, if only the base of the ventricle is active, it makes no difference to the electrocardiogram whether the inactive apex is not stretched (in a

bloodless heart) or whether it is being stretched as a heart hernia. Third, it is most improbable that the local stretching, like the S-T deviation, would reach a maximum in about one hour and would then, like the S-T deviation, begin to decrease, since it is generally accepted, at least in man, that the weakness of the ventricular wall is at its height during the second week after the obstruction of a coronary artery.<sup>23</sup>

On the basis of our observations, our study of the literature, and the experiments to be described further below, we prefer the following explanation of the S-T deviation, in which the decrease of this deviation need not parallel restoration of the local disturbances of function.

As a result of the local disturbance of circulation, local damage is done to the muscular tissue of the heart. This local damage which, even if incomplete, may eventually manifest itself in changes visible with the microscope,<sup>24, 25</sup> but which certainly does not do so in the early stages of its existence, discloses itself electrobiologically by a local depolarization of formerly polarized cell membranes, and therefore by increased permeability, decreased contractility, and, at this time most important of all, the local development of a relative electronegativity.<sup>26-30</sup> This local electronegativity produces a current of injury which, as is the case with all injury currents, exists only temporarily.

The S-T deviations which, as we have described, develop quickly, maintain a definite direction during their existence, reach their maximum in about one hour, and finally tend to disappear, result from the presence of this current of injury in a way that is discussed below.

Several articles concerning injury currents in the heart have appeared in the literature,<sup>31-37</sup> but, as far as we know, only few experiments have been made in that direction in connection with circulatory disturbances. Simon<sup>38</sup> found in the skeletal muscles an increased permeability in muscular asphyxia; Embden<sup>39</sup> the same in fatigue; and Wood and Wolferth<sup>4</sup> found that in a dog's heart after arterial ligation the electrogram recorded by direct leads from the damaged part quickly altered even when no changes were yet visible in the indirect leads. Very recently Johnston, Hill, and Wilson<sup>40</sup> showed by direct leads from the dog's heart that within some minutes after ligation the region supplied by the ligated vessel yielded a monophasic curve, from which finding they conclude that the muscle was capable of producing a large current of injury.

Before this last paper was published we investigated whether indeed by disturbances in the circulation an injury potential would develop in the monkey heart, which as with every other injury potential would be especially observable during rest, in the case of the heart then during diastole. The following experiment may be described as typical:

A *Macaca* heart was perfused according to the method of Langendorff with oxygenated Ringer-Locke solution. A nonpolarizable Porter electrode (A) was placed

in contact with a part of the conus arteriosus previously rendered maximally negative by cauterization. A second electrode (*B*) was connected to a healthy part of the left ventricular apex, also by means of a woolen thread soaked with saline (see Fig. 5). Connections with the galvanometer were such that the negative potential of *A* caused the shadow of the string, projected on a scale, to be deflected to the left. In order to neutralize this negativity, compensation was applied according to the method of Poggendorff, so that the compensating current as such moved the string to the right. If now during diastole *B* becomes more negative—in other words, more isoelectric to *A*—the compensating current which in itself is kept constant will become relatively too strong and the position of the string will be shifted to the right during diastole. This is exactly what we observed after the circulation through the heart had been stopped, a procedure we preferred to ligation of an artery, in order to be certain

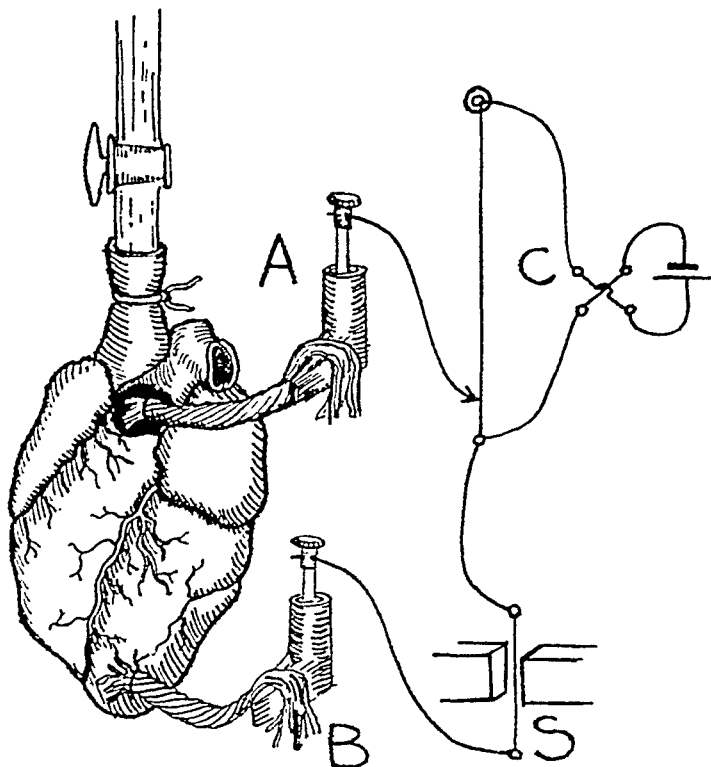


Fig. 5.—Showing arrangement used in experiment described in text. *A*, electrode in contact with burned part of conus arteriosus. *B*, electrode in contact with left apex, becoming temporarily more negative during diastole when circulation in isolated monkey heart is temporarily stopped. *C*, constant compensation; *S*, string.

that the electrode *B* would actually be in a region of disturbed circulation. After restoration of the circulation the diastolic position of the string again shifted in the direction of the original zero. The actual course of events is given here:

- 11:44 Circulation stopped.
- 11:46 String during diastole 5 mm. right of zero.
- 11:53 String during diastole 10 mm. right of zero.
- 11:56 String during diastole 10 mm. right of zero.
- 11:57 Circulation restored.
- 12:01 String during diastole 4 mm. right of zero.
- 12:03 String during diastole 2 mm. right of zero.

The string tension was such that 1 cm. = 4 mv.

In accordance with this, many curves of Samojloff<sup>32</sup> made by direct leads from the frog heart in comparable cases (damaging the apex by potassium chloride) without compensation show this diastolic displacement of the string quite clearly, for instance his curve 19, reproduced in our Fig. 6.

Also in the direct leads of Wood and Wolferth<sup>4</sup> the change in the curve, in our opinion, can be explained only as a consequence of an increasing diastolic negativity of the part of the heart involved in the circulatory obstruction, while also the recently published direct leads of Johnston and his coworkers<sup>40</sup> show this diastolic negativity in the dog's heart.

Theoretically it should be possible to observe this diastolic displacement of the string in electrocardiographic records made by indirect leads. Practically, efforts in this direction meet with special difficulties because of the inconstancy of the skin potential.

Our experiment on the isolated monkey heart, described above, showed that the diastolic displacement of the string developed progressively

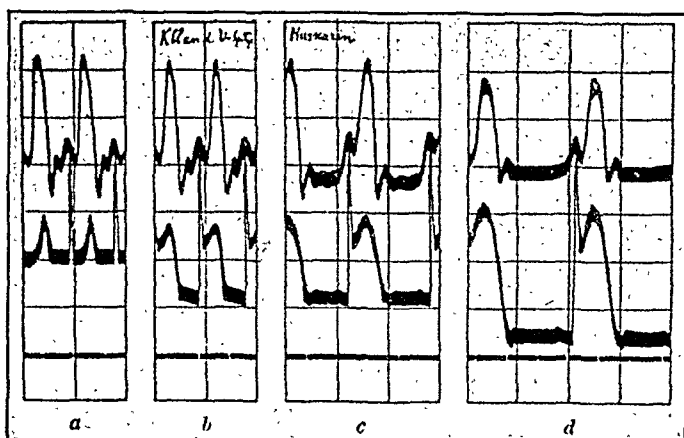


Fig. 6.—First parts of Samojloff's curve 19 described in text. Upper curve, mechanogram. Lower curve, electrogram, direct lead (frog heart). After the apex is damaged with potassium chloride, the string moves downward in diastole. The summit of R and the S-T deviation are in fact the last parts of the electrogram that are not displaced in this curve. No artificial compensation.

within a few minutes after stopping the circulation and tended to disappear again within a few minutes after restoration of it, provided that the circulation had not been stopped too long. This is in agreement with the speed with which the S-T deviation develops after coronary ligation and with which it disappears whenever the obstruction of the coronary circulation is removed after a sufficiently short lapse of time.

Such a reversibility of the deviation has been described in dogs and cats.<sup>4, 41</sup> In the monkey also this reversibility of the S-T deviation appears when the disturbance of the coronary circulation is of but short duration, as shown in the next experiment and in Fig. 7.

*Monkey AG.*—Leads I, II, and III of the electrocardiogram were recorded simultaneously before the operation (A). The opening of the thorax followed. The descending anterior branch of the left artery was closed off by means of a metallic skin clip, and the thorax was closed after the relations of the pericardium and lungs had been restored. The animal thereafter respired spontaneously. After 8 and 10



minutes records were taken (*B* and *C*). These records showed a distinct S-T deviation in all leads. A second operation was then performed. The clip was removed after the artery had been occluded for a total of 14 minutes. The thorax was then closed for the second time and again respiration became spontaneous. Records (*D*, *E*, and *F*) were now made 5, 7, and 11 minutes after restoration of the circulation. The S-T deviation disappeared progressively.

The observations described give an experimental basis for our opinion that the S-T deviations after coronary obstruction are a sign of the development of a local injury potential. This injury potential will mani-

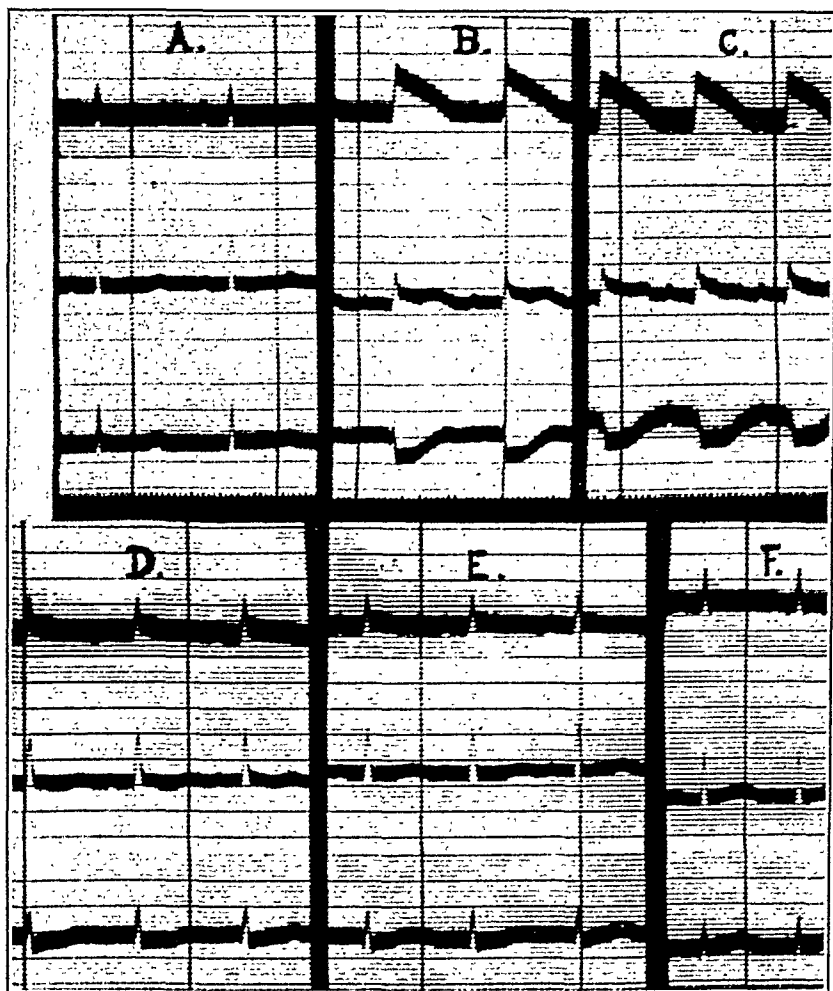


Fig. 7.—Mac. AG (L) Leads I, II, and III simultaneously. *A*, before operation; *B*, 8 min., *C*, 10 min. after the ramus descendens anterior was clamped off. *D*, 5 min., *E*, 7 min., and *F*, 11 min. after clamp was removed. All photograms taken with closed thorax and spontaneous respiration.

fest itself fully during diastole as an injury current. During systole this current of injury will diminish or disappear because at that time the contracting uninjured parts of the heart will also become electro-negative.\*

\*If, during the registration, the diastolic current of injury is artificially compensated, the compensating current during systole will lose its counterbalance. This compensating current will therefore manifest itself especially during systole, which for the deflection of the galvanometer is equivalent to a systolic disappearance of the current of injury.

In this regard the damaged heart will behave as a damaged muscle in general, which also shows its action current as a negative variation of its current of injury and tries to neutralize its current of injury during contraction. The principle is clearly illustrated by an old, but in this respect beautiful, record of Waller<sup>42</sup> which we reproduce in our Fig. 8.

That a current of injury must be considered as a possible factor in the etiology of the early electrocardiographic changes has been stated by others<sup>24, 43, 44, 45</sup> who, however, as far as we know, have made no quantitative directional measurements. Samojloff<sup>46</sup> suggested an area of permanent activity ("permanente Erregungszône") as a possible cause, which electrobiologically equals a lesion.

The injury current of the heart, manifest especially during diastole, depends upon an injury potential difference of *definite size and direction*. This size and direction will depend upon the intensity and site of the lesion. The S-T deviation is the manifestation of an effort on the part

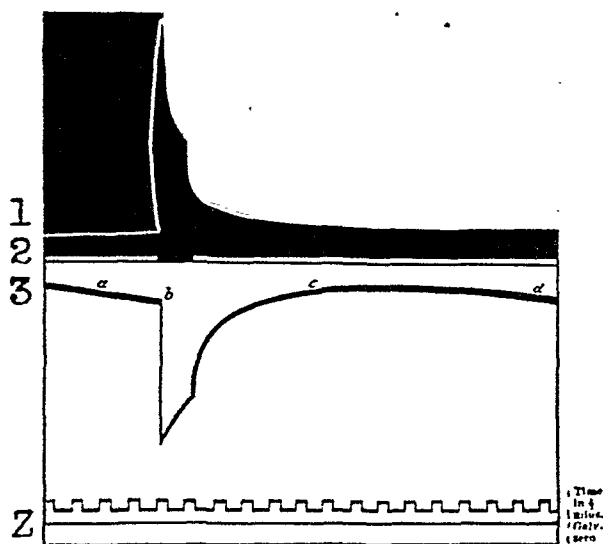


Fig. 8.—Upper curve, tetanic contraction of frog gastrocnemius. Second curve, signal of stimulation. Third curve (black line); accompanying negative variation of current of injury during tetanus. Below, time in  $\frac{1}{2}$  min. and zero line of galvanometer (Z). The slope from a to d shows the "natural" decrease of the injury current. (After Waller.)

of the injured heart to reach an isoelectric state during systole, by which effort the string during systole will be moved to, or near to, its true zero position. In the normal heart the same effort to reach the isoelectric state occurs. The deviation as such appears only in the electrocardiogram of the injured heart because only in the latter is *the diastolic position of the string no true zero position*.

The systolic compensation by the heart of its own injury current must occur in the direction diametrically opposite to that in which the original current of injury flowed. The direction of compensation is shown by the direction of the S-T deviation, the construction or calculation of which we described before. *Therefore, the direction of the electrical S-T axis will be the reverse of that of the original injury current*. For that reason it can contribute to our knowledge of the site of the lesion.

Our conception may be illustrated with the assistance of Fig. 9.

On the basis of our observations, the manifest direction in the heart of an injury current caused by a lesion of the left ventricular wall may, in the scheme of the equilateral triangle, be assumed to be from the lesion toward the center of the triangle—for instance from  $P$  to  $Z$ . The systolic compensation, whether complete or incomplete, will have to be in the diametrically opposite direction, namely, from the center of the triangle to the lesion, from  $Z$  to  $P$ . As the direction of compensation is represented by the direction of the electrical S-T axis, this latter must point to the lesion, or at least to the electrical center of the lesion.

In Fig. 9, therefore, the deviations  $+d_1$ ,  $+d_2$  and  $-d_3$ , combined according to the triangle scheme, give the direction from  $Z$  to  $P$  in which the heart tends during systole to neutralize the injury current, pointing in the direction of the lesion and in each lead in the direction of the

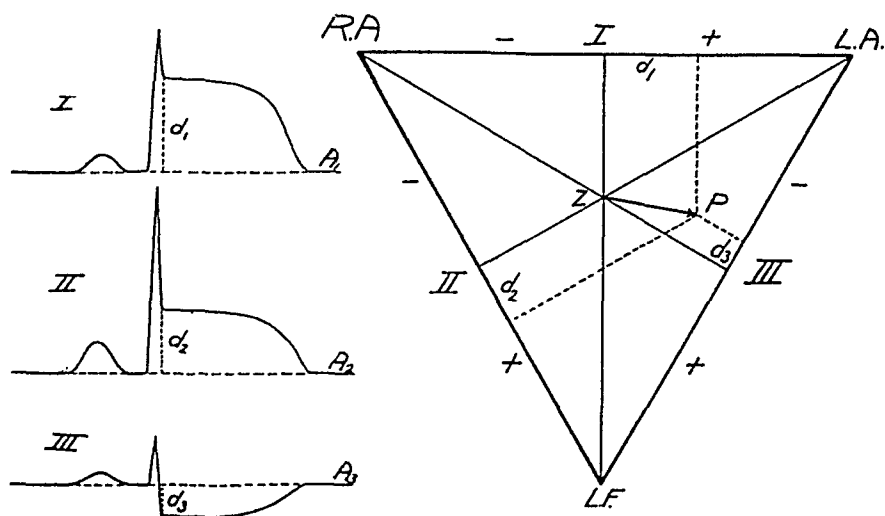


Fig. 9.—Diagram of an electrocardiogram with S-T displacement. The S-T deviations  $+d_1$ ,  $+d_2$  and  $-d_3$ , combined in the equilateral triangle, show the direction  $ZP$ , wherein the heart tries to compensate its current of injury, constituting the electrical S-T axis. The injury current passes the heart during diastole from  $P$  to  $Z$  and is the cause of the diastolic displacements  $-A_1$ ,  $-A_2$  and  $+A_3$ . Further details in text.

true zero position of the string. The diastolic position of the string ( $A_1$ ,  $A_2$ , and  $A_3$ ) does not represent an isoelectric condition of the heart; in fact, the string is then deviated, in  $A_1$  and  $A_2$  downward, in  $A_3$  upward, by the injury current which at that time is flowing in the heart from  $P$  to  $Z$  at its full strength.

It must now be explained why we take for measuring the direction of the S-T deviation that point in the electrocardiogram at which the deviation springs from the QRS complex.

For taking this point we have the following reasons:

First, this point, at which the curve undergoes an entire change in contour, is usually synchronous in all three leads, so that it may be used even if the records were not made simultaneously.

Second, at this point we are nearest to the instant at which in a normal heart the string returns to the zero line, since by that time the entire ventricular musculature has entered into a state of activity and in the normal heart no further measurable differences in potential exist. It is therefore a logical assumption that in the injured heart at that instant the compensation of the injury current has been established as completely as possible by as complete as possible a ventricular action. At that instant the direction of compensation will then be exposed at its clearest.

Third, as the QRS complex precedes the ejection phase of systole,<sup>33, 34, 47</sup> at the chosen instant no change in form of the heart has as yet taken place; and, on the other hand, there is yet no disactivation of fibers, each of which events might give rise to changes in the S-T axis, for instance, by a displacement of the lesion or by the development of complicating potential differences (for example, interference with a concealed T-wave).

A fourth reason for taking this point is based upon the following line of thought:

In order to explain the normal electrocardiogram, several theories were based on experimental evidence. The most prominent of these theories are those of the "distributed potential differences" and of the "limited potential differences." The first considers the heart as an electrical whole; the second considers the heart muscle fibers as individual electrical units.<sup>33, 35</sup> At this juncture we do not wish to give preference to either of these theories but merely to make the following remarks.

Above in explaining the significance of the S-T deviation after coronary ligation and the meaning of its direction, we paid particular attention to the relationships of the distributed potentials. However, if we choose the above indicated moment in the electrocardiogram for making the measurements, the explanation may be based also on the second theory. For it seems probable that at that moment, *which marks the beginning of the abnormal part of the electrocardiogram*, the action wave, having advanced along the septal conduction system and having penetrated the ventricular walls from within outward, will encounter the damaged fibers at the boundary of the lesion. According to the theory of the limited potential differences, in our opinion, it must be expected that the compensation of the injury current will principally occur by the activation of the uninjured portions of the damaged muscle units, the point of beginning of the deviation in the electrocardiogram then indicating the moment of that activation. In that case too, this compensation, resulting from a negative charge travelling through the ventricular wall from the subendocardial layers outward, must point from the center of the heart to the lesion.

This latter supposition would agree well with the fact observed by others<sup>48</sup> and very distinctly also by us, that in these experimental heart infarcts the subendocardial

\*Confirmed by Dr. H. Müller.

layers of the heart muscle are usually spared.\* We believe that this must be attributed to the nourishment of those layers directly from the heart cavity, either by diffusion or by the Thebesian vessels. That the action wave in such cases should penetrate the ventricular wall originally undisturbed, till it clashes with the lesion, appears to us entirely logical.

The above mentioned considerations of this subject give, in our opinion, a general understanding of the direction of the S-T axes found in our left and right monkeys.

That these axes, although limited to certain definite fields, do not all coincide in those fields must be expected in connection with various incidental factors, such as:

1. The imperfections in our measurements, partly caused by the difficulty of permanent perfect standardization;
2. The differences in position of the lesions
  - a. as a result of individual differences in the course and diameter of the coronary branches,
  - b. as a result of individual differences in the speed of development of the lesion on the one hand and of the collateral circulation on the other,
  - c. as a result of individual differences in the position of the heart in the thorax, partly increased by differences in respiratory phases;
3. Possibly individual differences in conduction rate in various parts of the heart.

That the *site of the lesions* varied in the different monkeys has already been mentioned in some detail in Part I. To show this in a more compact way we composed the next Fig. 10. In this figure the approximate site of the mass center of the lesion of each monkey heart is indicated, as far as these lesions were found in the ventricular wall with the aid of the microscope.

In seven equidistant parallel planes, perpendicular to the heart axis, the cross-section of each lesion was drawn. The center of such a cross-section was determined and the general center of the whole mural lesion was estimated by taking into consideration the difference in size of the cross-sections found in the separate planes. After these approximate centers were entered into the scheme, each was provided with an arrow indicating the direction of the concomitant S-T axis and with the number of the monkey concerned. In our opinion the position of the center of a lesion during first development will be about the same as that of the center of the lesion shown finally microscopically, since, as described in Part I, the S-T axis of the same monkey, taken at various intervals after operation, shows, as a rule, a tendency to keep a constant direction.

In Fig. 10 is also indicated which of the animals showed septum lesions.

Also from this figure it appears that the S-T axis, especially in those monkeys which showed no septum lesion, points from the center of the heart to the lesion.

We have already described a "mixed field," reaching from  $+90^\circ$  to  $+127^\circ$ , in which the S-T axes of right and left monkeys overlapped. Among the 5 left monkeys, the axis of which fell in this "mixed field," 3 certainly (6 L, 19 L, and 51 L) and 1 probably (16 L, bundle-branch block) had a lesion of the septum; while of the 9 monkeys in which septum lesions were found (6 left and 3 right monkeys, see Part I) 5 monkeys (3 left and 2 right) showed axes falling in this sector, which after all occupies only about one-tenth of the total field of  $360^\circ$ . We should not be surprised if further studies should confirm the idea that, especially in left monkeys, as S-T axis falling in this sector is a sign of a septum lesion.

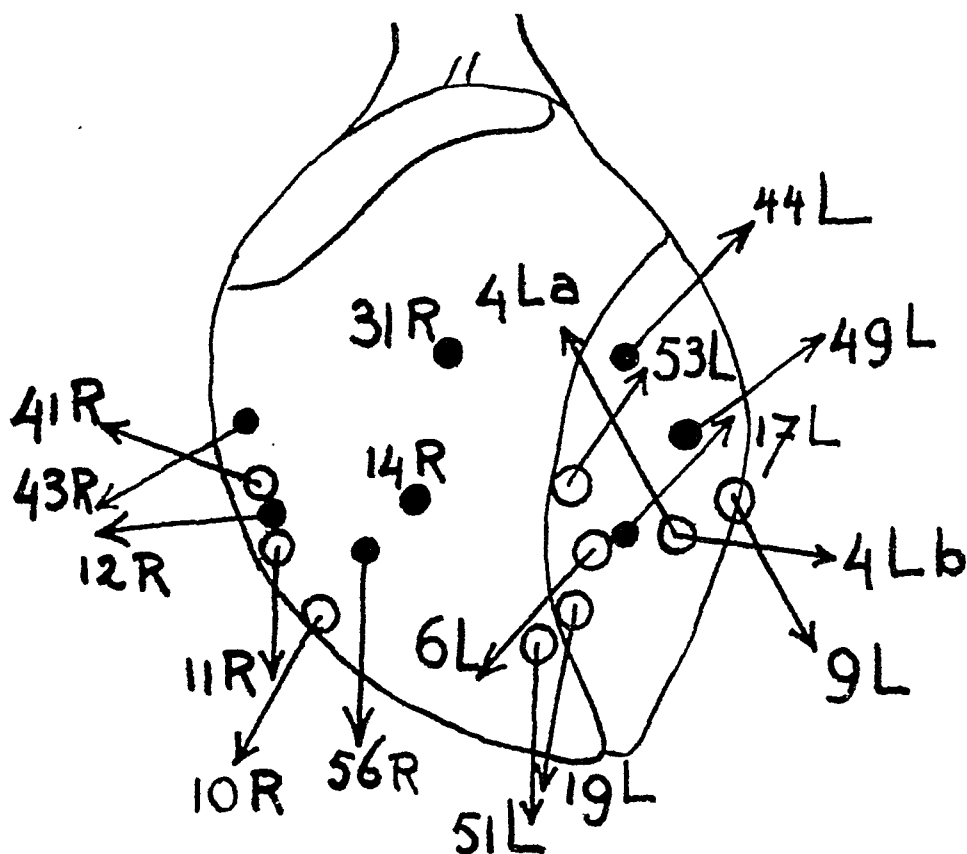


Fig. 10.—An approximate survey of the mass centers of the lesions of the ventricular wall, as far as these lesions finally showed morphologically. The arrows represent the direction of the electrical S-T axis during development of the lesions. Macaca 14 R and 31 R (frontal lesions) showed no S-T displacement. Septum lesions found in monkeys marked ○, no septum lesions in those marked ●. Further details in text.

In this connection the peculiar shifting of the S-T axis observed in Monkey 4 L and described in Part I may perhaps be explained. This animal had a septum lesion and developed an aneurysm in the left ventricular wall. One would be tempted to associate the first phase (4 A :  $-117^\circ$ ), directed to the base, with the septum and the second phase (4 B :  $+5^\circ$ ), directed to the left, with the developing aneurysm.

It is, however, also possible that the basally directed tangential components of the action current produced by the ventricular wall, the existence of which components was accepted on theoretical grounds,<sup>49</sup> may be held responsible for the pointing of some of our axes toward the base.

In considering our results, it should be remembered that in *Macaca* the heart and septum lie in the thorax in a position far more comparable to that in man than in other experimental animals, as for instance in dogs. The electrical axis of the heart of this monkey, measured at the summit of the R-wave, makes an average angle of  $63^{\circ}$  with the horizontal, but variations between  $50^{\circ}$  and  $75^{\circ}$  may easily be found.<sup>50</sup> In several frozen sections we observed that the septum makes as a rule an angle of about  $65^{\circ}$  with the horizontal, which certainly also may differ in various cases.

We have already mentioned that two of the right monkeys (14 R and 31 R) showed no S-T deviation. We attribute this to the frontal position of the lesions, described before and reproduced in Fig. 10.

As is known, the standard leads give information only about the electrical potential changes as projected on the frontal plane. Potential variations perpendicular to that plane, whether they be the result of action or of injury, are not observable. In *Macaca* the anterior part of the right ventricle, and especially the part near the conus arteriosus, lies in such a position that it is highly probable that lesions in those regions, such as were present in Monkeys 14 R and 31 R, would manifest themselves either not at all or only in part in these leads. The injury current and its compensation will in those instances be directed practically perpendicularly to the frontal plane.

We believe that the same inefficient condition pertains to the diametrically opposite part of the heart, namely, the posterior wall of the left ventricle near the sulcus longitudinalis posterior.

In this sense the frontal anterior or frontal posterior regions may be considered as "silent areas" of the heart when only the conventional leads are used.

In our experiments no isolated lesions of the posterior heart wall were obtained since in *Macaca* it is supplied principally by the circumflex branch of the left artery, which was not ligated. We shall make further investigations in this direction. In our opinion, however, it is to be expected on theoretical grounds that lesions, which are mirror images of one another in relation to a frontal plane passing through the hypothetical center of the heart, should give similar electrocardiographic changes because of the similar projection of their electrical components on that plane.

Figure 11 may serve to illustrate this principle of "mirror image lesions."

Some authors are of the opinion that in man lesions of the posterior wall of the left ventricle near the septum could, even if the right ventricle is intact (which is often questionable<sup>51</sup>), produce S-T deviations directed downward in Lead I.<sup>24, 52, 53</sup> Such lesions could, as is mentioned by Barnes and Whitten,<sup>52</sup> sometimes behave as lesions of the right ven-

tricle. This would be entirely in agreement with our point of view whenever a position of the heart may be assumed as reproduced in Fig. 11.

The classical leads therefore will probably be unable to differentiate between such mirror image lesions. On theoretical grounds it may be expected that antero-posterior or precordial leads<sup>4, 37, 54, 55, 56</sup> will be of value in such cases. We have, as yet, no practical experience in this direction.

The gradual *disappearance of the S-T deviation* must, in our opinion, be explained in the following way:

It is well known that injury currents have only a temporary existence and that they decrease and disappear within a rather short time, espe-

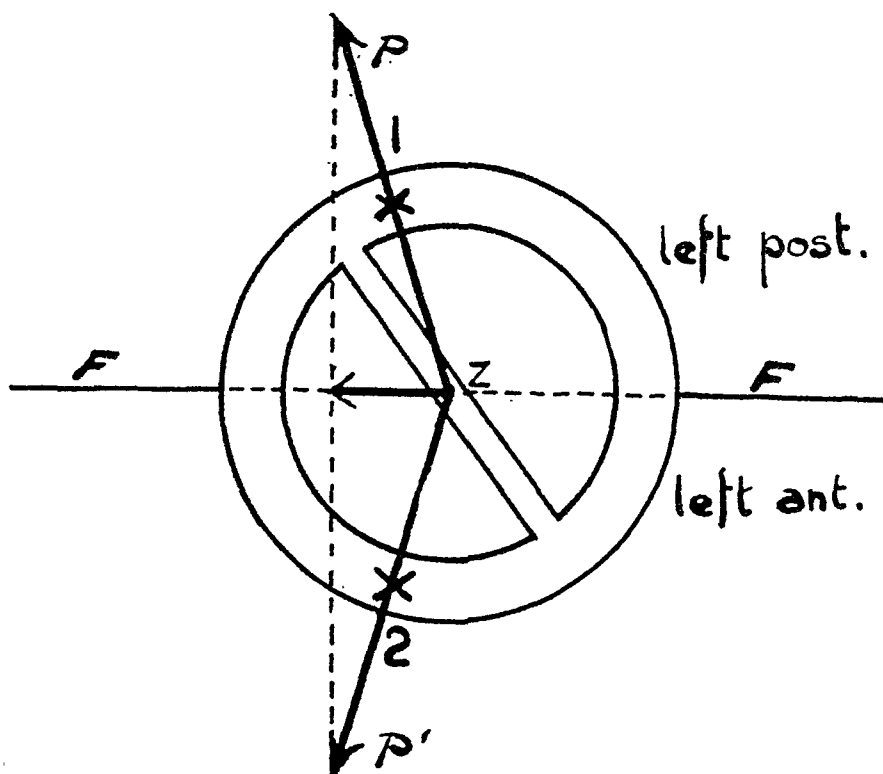


Fig. 11.—Showing the principle of the mirror image lesions described in text. The lesions, 1 and 2, in posterior part of left ventricle and anterior part of right ventricle may give a similar S-T deviation, this deviation (direction of systolic compensation of current of injury) being determined in the conventional leads by the projection, that  $ZP$  and  $ZP'$  have in common, on the frontal plane  $FF$ .

cially in the heart.<sup>26, 32, 33, 34, 57</sup> We have already shown this phenomenon in a skeletal muscle in Fig. 8.

Whenever in the heart the injury potential—in other words, the local relative negative potential—disappears, the S-T deviation will disappear. In the case of disturbances of short duration (Fig. 7) this occurs because the entire process in the cells is still reversible and therefore the tissue elements return to their original condition and function without permanent changes having developed. In disturbances of longer duration that give rise to permanent local anatomical and functional changes, it occurs presumably because the remaining muscle substance is again enclosed by polarized membranes; while the developing connective tissue



cells, which furthermore are not concerned in the transmission of the action wave, must also be considered as being encapsulated by similar membranes. The demarcation after the injury is not the cause of the current of injury but is the cause of the disappearance of the current.<sup>26, 27</sup>

Therefore, it will be just the fresh, electrically active changes in the heart substance that will be able to give rise to definite S-T deviations. When the lesion has once become electrically inactive or less active, a new lesion must be able to impress itself upon the electrocardiogram, as we observed in Monkey 6 L + R and as is perhaps also present in Monkey 4 L (types A and B).

How are the *after-waves*, which develop so frequently during the regression of the S-T deviation, to be explained?

As a rule those after-waves point in a direction opposite to the S-T deviation and are accompanied by a prolongation of the ventricular complex, i.e., the ventricular systole, so far as that is measurable in the electrocardiogram. Evidently, therefore, they are connected with a prolonged action of some part of the heart muscle (compare also<sup>32, 58</sup> and Figure 235 given by Einthoven<sup>33</sup>). Considering that the direction of the after-wave is opposite to that of the S-T deviation, in other words that it is the same as that of the original current of injury, it seems possible that the after-wave must be attributed to a prolonged negativity of muscle elements near the lesion, i.e., a prolonged activity of muscle parts of especially that side of the heart where the lesion developed.\*

It is known of both heart and skeletal muscle that under mechanical overloading or after various functional injuries, such as in aortic stenosis,<sup>59</sup> enlarged venous inflow,<sup>60</sup> and fatigue,<sup>61</sup> the contraction is prolonged, particularly in the phase of relaxation. It is possible that a comparable prolongation of contraction occurs in the hearts in question since a resistance in the circulatory system, in itself normal, may mean an increased resistance to an injured heart. The remaining muscle mass of the damaged ventricle may possibly need more time to bring the original systolic blood volume to the original pressure, and to eject it, than was needed formerly by the undamaged ventricle. A prolongation of systole may also point to increased initial tension and diastolic size.<sup>3</sup> It is also quite conceivable that in some cases processes of compensatory hypertrophy, which we have often believed present in the remaining parts of the damaged ventricle, play a rôle and lead to a prolongation of conduction and activation.<sup>62</sup>

Whatever the truth may be, in our opinion the after-wave is to be regarded as the expression of a heart action altered in consequence of the loss of former muscular elements. Further insight into the exact meaning of this wave will be obtainable only when through the applica-

\*The theory of the limited potential differences leads to interpreting the after-wave as a late retreat of the excitation wave in fibers which produce during activation a deflection in the opposite direction of the after-wave, i.e., in the direction of the S-T deviation. This would then also mean a late disactivation of fibers in the neighborhood of the lesion.

tion of adequate physiological methods a further investigation is made of the functional changes of various parts of the heart, not only in the acute phase, but also during the period of cicatrization.\*

We found that the after-wave as a rule was not accompanied by an increased duration of the QRS complex and, even if septum lesions were absent, not by a definite change in this complex. In our opinion this indicates that the components of the electrocardiogram, however one may consider them, are not shifted in their initial phases, so that probably some, beginning at their original time, are prolonged with or without a change in their detailed configuration.

The following *final remarks* may serve to prevent any misunderstanding.

Solely for the sake of brevity we have used here and there the term "coronary electrocardiogram." We wish to point out that, although on the basis of our experiments and observations we regard the cause of the S-T deviations discussed before to be a lesion manifesting itself electrically and although it seems to us to be permitted to extend this conclusion to comparable cases in human pathology, we do not mean to say that each and every displacement of the S-T segment in any given electrocardiogram must necessarily point to a disturbance in the coronary flow or to a locally developed injury potential.

The explanation of the fact that the S-T segment usually belongs to the equipotential parts of the normal electrocardiogram is not known with absolute certainty. In the literature<sup>33</sup> two possibilities are suggested:

1. All the heart muscle elements are in complete contraction so that there is no potential difference in any of them and thus no action current flows through the galvanometer.
2. There are indeed potential differences present in the heart muscle, but they happen to balance out, so that the manifest resultant of all potential differences in the customary leads happens to be zero.

Now it is a common experience that sometimes in man small deviations of the S-T segment from the diastolic line may be observed without there being any reason to suspect the presence of a pathological heart or of an injury current.† In several of Einthoven's classical "normal" curves they are also to be found. Is there in such an instance no period of collective contraction of the muscle elements, or do potential differences of such direction and size develop that a measurable resultant remains? Or have certain potential differences either not developed at all, or to a smaller degree, or in other time relationships? Can this occur to a cer-

\*The recent work of Wilson, Hill, and Johnston,<sup>33</sup> made by direct leads in the dog's heart, considers the disappearance of the electrical forces formerly produced by the muscle part deprived of its blood supply as concerned in the later changes of the electrocardiogram.

†We do not deny the possibility of the existence of such small physiological variations in monkeys, but we have not seen them with certainty and, in our opinion, they play no part in the observations we have described.

tain extent in a healthy heart? Is it in this direction that an explanation must be sought for S-T displacements when the contractions of left and right ventricle are shifted in time, as in extrasystoles and conduction disturbances,<sup>64</sup> S-T deviations such as described in heart strain,<sup>65</sup> and under the influence of digitalis<sup>66</sup>? In both of these last groups of cases, however, lesions are also often found.<sup>25, 67</sup> Are displacements of the S-T segment as seen in rheumatic fever,<sup>68, 69</sup> pericardial effusion,<sup>70, 71</sup> anoxemia,<sup>72-75</sup> yellow fever<sup>76</sup> based on the influence of an injury current as are those after coronary obstruction?

In all such cases it will, in our opinion, be useful to determine the direction of the S-T axes and to look for a correlation with definite disturbances in the heart muscle and heart function.

It is not our intention to enter further into these still outstanding problems at this time.

#### SUMMARY

A further study was made of the acute results of coronary ligation on the functional conditions of the heart in the Javanese monkey (*Macaca irus*). In general, no acute dynamic changes in the action of the heart as a whole could be found after ligation. Therefore such changes cannot be the cause of the S-T deviations observed in such cases. Experiments on the isolated monkey heart lead one to accept the view that probably a local hypofunction, perhaps preceded by a short local hyperfunction, occurs in the portion of the heart deprived of its blood supply. The time relationships, however, show that they cannot be the cause of the S-T deviations observed. A depressed conduction or a deformation current is also excluded as a possible cause of the S-T deviation after ligation. The S-T deviation after ligation is explained to be, in its time relationships and its direction, the result of the development, temporary existence, and successive disappearance of a current of injury. The direction of the current of injury in the heart depends upon the site of the lesion. The direction of the S-T axis is the reverse of that of the original injury current and results from systolic compensation of this injury current. The string is deflected or influenced by the injury current especially during diastole. The development of a local electronegativity during diastole was observed in experiments on isolated monkey hearts, the coronary perfusion of which was interrupted. This local electronegativity proved to develop quickly and to be reversible in the isolated heart in case of circulatory disturbance of short duration. The same quick development and reversibility proved to be present in the S-T deviation of a monkey during and after occluding the anterior descending branch for a short time. Reasons are given why, for determining the direction of the S-T axis from the electrocardiogram, that point is taken at which the deviation springs from the QRS complex. The relation of the site of the lesions to the direction of the S-T axis is described. Septum lesions probably tend to cause an S-T axis in the

"mixed" sector. Frontal lesions may occur without S-T deviations in the conventional leads. The principle of the "mirror image lesions" is described, being lesions in opposite parts of the heart which, by similar projection of their electrical components on a frontal plane, give similar electrocardiographic changes and therefore cannot be differentiated in the standard leads. Disappearance of the S-T deviation is attributed to disappearance of the current of injury, which fact may or may not mean restoration of function. Especially the fresh, electrically active lesions will be able to produce S-T deviations. The after-wave is probably the result of a prolonged action of fibers in the neighborhood of the lesion. Not every displacement of the S-T segment in any given electrocardiogram must necessarily indicate a disturbance of the coronary flow or a local development of an injury potential.

## REFERENCES

1. De Waart, A., Storm, C. J., and Koumans, A. K. J.: Ligation of the Coronary Arteries in Javanese Monkeys. I. Introduction, General Experimental Results, Especially the Changes in the Ventricular Electrocardiogram, *AM. HEART J.* 11: 676, 1936; II. Arrhythmias and Conduction Disturbances, *AM. HEART J.* 12: 70, 1936.
2. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, I, *AM. HEART J.* 6: 522, 1931.
3. Orias, O.: The Dynamic Changes in the Ventricles Following Ligation of the Ramus Descendens Anterior, *Am. J. Physiol.* 100: 629, 1932.
4. Wood, F. C., and Wolferth, C. C.: Experimental Coronary Occlusion, *Arch. Int. Med.* 51: 771, 1933.
5. Sands, J., and de Graff, A. C.: The Effects of Progressive Anoxemia on the Heart and Circulation, *Am. J. Physiol.* 74: 416, 1925.
6. Wiggers, C. J.: The Fractionate Nature of Ventricular Contraction and the Influence of Changes in Ventricular Conduction in the Form of the Pressure Curve, *Skandin. Arch. f. Physiol.* 49: 247, 1926.
7. Fletcher, W. M.: The Relation of Oxygen to the Survival Metabolism of Muscle, *J. Physiol.* 28: 474, 1902.
8. Tigerstedt, R.: *Physiologie des Kreislaufes* 1: 286, 1921.
9. Strughold, H.: Cinematographic Study of Systolic and Diastolic Heart Size With Special Reference to Effects of Anoxemia, *J. Physiol.* 94: 641, 1930.
10. Dale, A. S.: The Relation Between Metabolic Processes and the Ventricular Electrogram, *J. Physiol.* 84: 433, 1935.
11. Van Dyk, J. A.: The Influence of the Blood Supply Upon Muscular Activity in Birds, *Arch. neerl. de Physiol.* 18: 387, 1933.
12. Rothberger, C. J.: *Kreislauf*, in Lüdke, H., and Schlayer, C. R.: *Lehrbuch der path. Physiol.* p. 368, 1922.
13. Lewis, T.: *Diseases of the Heart*, 1934, p. 43.
14. Otto, H. L.: The Effect of Obstruction of Coronary Arteries Upon the T-Wave of the Electrocardiogram, *AM. HEART J.* 4: 346, 1929.
15. Robb, J. Sands: Progressive Muscular Anemia in the Heart of a Dog, *Proc. Soc. Exper. Biol. & Med.* 31: 761, 1934.
16. Otto, H. L.: The Extracardial Nerves, IV. An Experimental Study of Coronary Obstruction, *AM. HEART J.* 4: 64, 1929.
17. Wiggers, C. J.: *Circulation in Health and Disease*, ed. 2, Philadelphia and New York, 1923, p. 429.
18. Wiggers, C. J.: Monophasic and Deformed Ventricular Complexes Resulting From Surface Applications of Potassium Salts, *AM. HEART J.* 5: 346, 1930.
19. Tennant, R., and Wiggers, C. J.: The Effect of Coronary Occlusion on Myocardial Contraction, *Am. J. Physiol.* 112: 351, 1935.
20. de Meyer, J.: Sur un nouveau concept electrophysiologique, *Arch. neerl. de Physiol.* 7: 292, 1922.
21. Gilson, A. S.: The Monophasic Action Potential Curve of Tortoise Ventricular Muscle, *Am. J. Physiol.* 82: 533, 1927.
22. de Boer, S.: The Electrogram of the Ventricle, *Am. J. Physiol.* 74: 158, 1925.

23. Lewis, T.: Diseases of the Heart, 1934, p. 46.
24. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
25. Büchner, F., and von Lucadou, W.: Elektrokardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimenteller Coronarinsuffizienz, *Beitr. z. path. Anat. u. z. allg. Path.* 93: 169, 1934.
26. Bernstein, J.: *Elektrobiologie*, 1912.
27. Osterhout, W. J. V.: Injury, Recovery and Death in Relation to Conductivity and Permeability, Philadelphia, 1922, J. B. Lippincott Company.
28. Fulton, J. F.: Muscular Contraction and the Reflex Control Movement, Baltimore, 1926, Williams & Wilkins Company.
29. Bayliss, W. M.: Principles of General Physiology, 639, 1927.
30. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Tissues, Immersed in Extensive Conducting Media, *J. Gen. Physiol.* 16: 423, 1933.
31. Samojloff, A.: Weitere Beiträge zur Elektrophysiologie des Herzens, *Arch. f. d. ges. Physiol.* 135: 417, 1910.
32. Samojloff, A.: Die Vagus und Muskarinwirkung auf die Stromkurve des Froschherzens, *Arch. f. d. ges. Physiol.* 155: 471, 1914.
33. Einthoven, W.: Die Aktionsströme des Herzens, *Handb. norm. u. path. Physiol.* 8: 2; 785, 1928.
34. Craib, W. H.: The T-Wave in the Electrocardiogram, London, 1930, His Majesty's Stat. Off.
35. Katz, L. N.: The T-Wave in the Electrocardiogram and Electrocardiogram, *Physiol. Rev.* 8: 447, 1928.
36. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, 1925, p. 58.
37. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction, I, *AM. HEART J.* 9: 596, 1934.
38. Simon, M.: Ueber den Einfluss der Erstickung auf den Permeabilitätszustand von Muskelfasergrenzschichten, *Hoppe-Seyler's Ztschr. f. physiol. Chem.* 118: 98, 1922.
39. Embden, G.: *Handb. d. norm. u. path. Physiol.* 8: 411, 1925.
40. Johnston, F. D., Hill, I. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction, II, *AM. HEART J.* 10: 889, 1935.
41. Wood, F. C., and Wolferth, C. C.: Angina Pectoris, *Arch. Int. Med.* 47: 339, 1931.
42. Waller, A. D.: Introduction to Human Physiology, 1896.
43. Clarke, N. E., and Smith, F. J.: Electrocardiogram in Coronary Thrombosis, *J. Lab. & Clin. Med.* 11: 1071, 1926.
44. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction, *Heart* 14: 195, 1928.
45. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface, I and II, *AM. HEART J.* 10: 163 and 176, 1934.
46. Samojloff, A.: Die Stromkurve des partiell durchschnittenen Froschventrikels und die Leitung im Herzmuskel, *Arch. f. d. ges. Physiol.* 222: 516, 1929.
47. Wiggers, C. J.: The Independence of Electrical and Mechanical Reactions in the Mammalian Heart, *AM. HEART J.* 1: 3, 1925.
48. Robertson, H. P.: The Reestablishment of Cardiac Circulation During Progressive Coronary Occlusion, *AM. HEART J.* 10: 533, 1935.
49. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, *AM. HEART J.* 6: 637, 1931.
50. de Waart, A., and Storm, C. J.: Electrocardiographic Observations on Javanese Monkeys, *Act. brev. neerl.* 4: 130, 1934, and *Arch. neerl. de Physiol.* 20: 255, 1935.
51. Büchner, F., Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz, Leipzig, 1935, Georg Thieme.
52. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1930.
53. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Myocardial Lesions by the Electrocardiogram, *AM. HEART J.* 7: 627, 1932.

54. Welferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
55. Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, *Arch. Int. Med.* 51: 947, 1933.
56. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
57. du Bois Reymond, E.: Untersuchungen über tierische Elektrizität, 230, 1849.
58. Mines, G. R.: On Functional Analysis by the Action of Electrolytes, *J. Physiol.* 46: 188, 1913.
59. Katz, L. N., Ralli, E. P., and Cheer, S. N.: The Cardiodynamic Changes in the Aorta and Left Ventricle Due to Stenosis of the Aorta, *J. Clin. Investigation* 5: 205, 1928.
60. Katz, L. N.: Observations on the Dynamics of Ventricular Contraction in the Heart-Lung Preparation, *Am. J. Physiol.* 80: 470, 1927.
61. Fenn, W. O.: *Handb. d. norm. u. path. Physiol.* 8: 190, 1925.
62. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch. Int. Med.* 25: 146, 1920.
63. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction, III, *AM. HEART J.* 10: 903, 1935.
64. de Boer, S.: L'influence de la vitesse de conduction de l'excitation sur la forme de l'électrogramme ventriculaire, *Arch. neerl. de Physiol.* 3: 7, 1918.
65. Quincke, H.: Die Bedeutung der Nachschwankung im Elektrokardiogramm für die Beurteilung von Herzkrankheiten, *Deutsche med. Wchnschr.* 60: 595, 1934.
66. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T-Wave of the Human Electrocardiogram, *J. Exper. Med.* 21: 593, 1915.
67. Büchner, F.: Herzmuskelinfarkt und disseminierte Nekrosen des Herzmuskels, Vortrag Oeynhausen, 1933.
68. Colin, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* 39: 1, 1924.
69. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T-Wave in Rheumatic Pericarditis, *AM. HEART J.* 4: 584, 1929.
70. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion, *AM. HEART J.* 5: 68, 1930.
71. Bay, E. M., Gordon, W., and Adams, W.: Electrocardiographic and Blood Pressure Changes in Experimental Pericardial Effusion and Occlusion of the Venae Cavae, *AM. HEART J.* 8: 525, 1933.
72. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1930.
73. Dietrich, S.: Blutversorgung und Aktionsstrom des Herzens, *Ztschr. f. d. ges. exper. Med.* 90: 689, 1933.
74. Kountz, W. B., and Hammouda, M.: The Effect of Asphyxia and of Anoxemia on the Electrocardiogram, *AM. HEART J.* 8: 259, 1932.
75. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, *AM. HEART J.* 9: 771, 1934.
76. Wray, Lloyd: The Myocardium in Yellow Fever, *AM. HEART J.* 6: 483, 1931.

# PULMONARY INSUFFICIENCY WITH A SUPERNUMERARY CUSP IN THE PULMONARY VALVE

REPORT OF A CASE WITH REVIEW OF THE LITERATURE\*

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A CASE is reported here of a patient who during life suffered from pulmonary insufficiency and whose heart at necropsy presented four pulmonary cusps and commissures. Four pulmonary cusps as an accidental post-mortem finding occurs once in a thousand necropsies but, combined with clinical insufficiency of the valve, only three definite cases have previously been reported. Nevertheless, investigation of the literature indicates that the clinical diagnosis of the valvular anomaly might be made more frequently, and it is for this reason that the case and a survey of the literature are presented.

## REVIEW OF LITERATURE

Reports of 151 cases of hearts with four pulmonary cusps were found in the literature. Further, through the courtesy of Dr. Maude E. Abbott, it is possible to include three additional cases from the Medical Museum of McGill University,<sup>1</sup> making a total of 154 cases.

Most of the reports of these 154 cases were purely anatomical, giving no information as to the patients' clinical statuses. However, in 24 cases mention was made of the presence or absence of physical signs of pulmonary insufficiency during life. Of these 24 cases, in 3 there was clear clinical evidence, in one possible evidence, and in 20 no definite evidence of pulmonary regurgitation. All 3 cases in which there was clear evidence of pulmonary incompetence during life, likewise included evidence at necropsy. In the one case in which there was possible evidence of clinical insufficiency, no mention was made of anatomical insufficiency. Of the 20 cases in which no signs or symptoms were observed, in 17 there was no evidence of valvular incompetency noted at necropsy, and in 3 cases a dilated pulmonary artery was found.

In addition to these cases, there were seven reports which failed to mention the physical findings during life, but in which evidence of pulmonary insufficiency was discovered at necropsy.

Begbie,<sup>4</sup> Bernabei<sup>5</sup> and Kolisko<sup>39</sup> reported the three cases in which definite evidence of pulmonary incompetence was observed during life.

\*From the Medical Service of the late Dr. Marcus A. Rothschild, Beth Israel Hospital, New York.

In Begbie's case,<sup>4</sup> a boy eighteen years old first consulted the physician because of shortness of breath aggravated by exertion. From earliest recollection he had been unable to run with other boys. There were present on examination a basal systolic thrill and a loud blowing systolic murmur along the left sternal border at the level of the third rib, followed by a diastolic murmur of lesser intensity. The systolic murmur radiated to the entire upper chest, whereas the diastolic was limited to the site of maximum intensity. At the age of twenty-one years the boy died of a fractured skull. The heart anomaly was discovered at post-mortem examination by Haldane.<sup>30</sup> There were three pulmonary cusps of ordinary size and a fourth which was smaller than the others and imperfectly separated from one of them. The water test showed slight incompetence of the valve. The other valves were normal, the heart was normal in size, and the right ventricle was not dilated.

In Bernabei's case<sup>5</sup> a man of fifty-four years died of "collapse" of the heart during a resolving pleuropneumonia. He had suffered from attacks of nocturnal asthma and palpitation for some time before his terminal illness. A soft, weak thrill was felt during systole and diastole. Over the area of the thrill was heard a harsh double murmur. The systolic murmur was the louder, being loudest at the apex. The diastolic murmur was softer and was loudest in the fourth intercostal space to the left of the sternum. The second pulmonic sound was clear and sharp. The second aortic sound was lower pitched and was followed by a faint short systolic blow. At necropsy the pulmonary artery appeared aneurysmal and measured 16 cm. in circumference at a distance of 3 cm. from its origin. There were four pulmonary cusps, of which three were of equal and normal size, and a fourth cusp which was of the same height and thickness but narrower.

In Kolisko's case<sup>39</sup> a woman of thirty-four years thought she was pregnant because of swelling of the abdomen, but actually she suffered from circulatory insufficiency, with ascites, which caused her death. She had suffered for many years from palpitation of the heart, and from time to time from pain in the chest and difficulty in breathing. She came into the hospital complaining of shortness of breath. Physical examination disclosed the evidences of circulatory failure; distention of the neck veins, cyanosis, dyspnea, ascites, and edema of the lower extremities. Systolic and diastolic murmurs were present. On admission, the systolic murmur was heard equally well over the apex and the base of the heart. The diastolic murmur was heard best at the left upper border of cardiac dullness. A week after admission both murmurs were heard only over the pulmonary area. A slightly patent foramen ovale was found at autopsy. There were four pulmonary cusps, of which three were normal in size, and the fourth about half as wide. The right auricle, right ventricle, conus arteriosus, and pulmonary artery were dilated.



Hodenpyl<sup>31</sup> reported the case in which possible evidence of pulmonary incompetence was observed during life. In this case a well-marked pre-systolic murmur was heard during life, but the location of the murmur was not given nor the anatomical findings other than the supernumerary pulmonary cusp.

In the cases of Cattell,<sup>14</sup> Klob,<sup>33</sup> and Thompson,<sup>68</sup> the hearts presented at necropsy dilated pulmonary arteries, but during life the murmur of pulmonary insufficiency was not heard.

The seven case reports in which evidence of pulmonary insufficiency was noted only at necropsy include the following. In Boettcher's sixth case,<sup>8</sup> necropsy revealed obvious insufficiency of the pulmonary valve. In Brüninghausen's second case,<sup>10</sup> a man aged sixty-four years suffered for years from shortness of breath. No examination of the chest was made before death. But at necropsy the right ventricle was found enormously dilated and the wall greatly thickened. In one of Dilg's two cases,<sup>22</sup> a year-old boy, who died of atelectasis of the lungs and intestinal catarrh, presented at necropsy a dilatation of the pulmonary artery and right ventricle. In Lindenberg's first case,<sup>44</sup> at post-mortem examination a wide pulmonary artery was seen. In Virchow's case<sup>72</sup> the right side of the heart (in a man of fifty-six years) was found greatly hypertrophied, and the pulmonary conus and artery were dilated. The pulmonary valve was incompetent. No clinical account accompanied this report. In one of Viti's two cases<sup>73</sup> a woman died in the sixth month of pregnancy following cardiopulmonary complications. Dilatation of the pulmonary artery and right ventricle and buttonhole mitral stenosis were found. One could not be certain of the cause of the arterial dilatation, whether it was secondary to the mitral stenosis or to the valvular anomaly. In Wauchope's second case<sup>76</sup> necropsy revealed a dilated pulmonary artery.

*Frequency.*—Dagnini<sup>18</sup> found 5 cases of four pulmonary cusps in 5,000 necropsies at the Institute of Pathological Anatomy of Bologna from 1925 to 1929, inclusive. De Vries<sup>21</sup> found 9 cases in 3,600 in Amsterdam. Houck<sup>22</sup> encountered 2 cases in 5,000 at the Massachusetts General Hospital. Simonds<sup>52</sup> found one case in 20,000 coroner's examinations in Chicago. Simpson<sup>64</sup> found 4 cases in 4,252 necropsies at the West Riding Asylum, Wakefield, England. Thilo<sup>67</sup> found 3 cases in 5,814 at Leipzig. In 23,416 necropsies, 24 cases of four pulmonary cusps were discovered.

*Sex and Age.*—Of these cases in which the sex was mentioned, 44 were in males and 25 in females. The age of the patients at death varied from five months to eighty years, the average being forty years. In no instance could one definitely attribute the death of the patient to the presence of the anomaly.

*Size and Site.*—Supernumerary pulmonary cusps may be classified according to size. There are cases in which one cusp is smaller and the other three larger and equal, cases in which one is larger and the other three smaller and equal, cases in which all the cusps are the same size, in which two cusps are smaller and two larger, and in which no two cusps are of the same size. Most of the cases, however, resemble the one here reported in that there are three larger cusps and one small one.

In many instances the supernumerary cusp is deformed, imperfect, or shrunken. Often it is fenestrated.

The site of the supernumerary cusp varies in that it may lie between the left and anterior, anterior and right, or left and right cusps.

#### REPORT OF CASE

F. E., a widow, forty-one years old, came to the out-patient department of Beth Israel Hospital in 1925 complaining of headache, shortness of breath, and palpitation on moderate exertion, of three years' duration. There was no history of rheumatism or syphilis.

Physical examination revealed a well-nourished woman who appeared comfortable. Her blood pressure was 205/140, the pulse rate 96, with occasional extrasystoles. The second aortic sound was accentuated. There was a soft systolic apical murmur.

In July, 1926, there was heard for the first time a *diastolic murmur* over the *pulmonic area*.

In February, 1928, she complained of shortness of breath, palpitation, and cough on slight exertion. A split first sound was heard at the apex.

In April, 1928, a faint diastolic blowing murmur and a rough systolic murmur were heard over the pulmonary area. The liver edge was palpable two fingerbreaths below the costal margin. The blood pressure was 224/110.

In November, 1928, ophthalmoscopy revealed retinal hemorrhages. At this time fluoroscopic findings (Dr. Nemet) were: triangular heart, moderate enlargement of the left ventricle, marked prominence of the pulmonary artery and conus, obliteration of almost the entire retrocardiac space, widening of the aorta.

The patient was admitted to the hospital for the first time on Sept. 24, 1929, complaining of persistent occipital headache, swelling of the ankles, palpitation, poor vision, and shortness of breath on exertion. For two months previous to admission she had been dyspneic on the slightest exertion, developing pounding of the heart and tingling and pain in the extremities. Further, with the dyspnea, she began to cough and to raise blood-tinged sputum.

There were scattered sibilant râles over both lung fields. The apex beat was palpable in the fifth left interspace; the heart rate was regular. There were present a blowing, soft, apical systolic murmur, a low-pitched basal systolic murmur, and a faint, high-pitched basal diastolic murmur. The blood pressure was 260/150.

Kidney function was good. The blood Wassermann test was negative. The roentgenogram of the chest (Fig. 1) showed congestion of both lungs, accentuation of the pulmonary conus, generalized enlargement of the cardiac shadow, and a heart shape characteristic of mitral valvular disease. Ophthalmoscopic examination showed retinal edema and hemorrhage.

The patient was discharged on Nov. 12, 1929, as improved.

*Second Admission.*—She was readmitted Jan. 6, 1930, having remained at home in bed from the time of discharge, two months before. Four days prior to admission the patient suffered a sudden severe headache which lasted for two days.

She had also precordial pain and palpitation and was dyspneic. The day before admission she awoke from sleep dazed, recognized no one, recalled nothing, but suffered no paralysis. The fingers of both hands developed a pins-and-needles sensation, and her entire left arm felt weak.

The blood pressure was 230/140. The heart rhythm was normal, and the heart was much enlarged. There was a rough systolic murmur at the base of the heart, heard best over the sternum; a faint diastolic murmur, heard best in the pulmonary area; and a faint systolic apical murmur. A few crepitant râles were heard over both lung bases. The liver edge was two fingerbreaths below the costal margin, and tender. There was no edema of the legs.

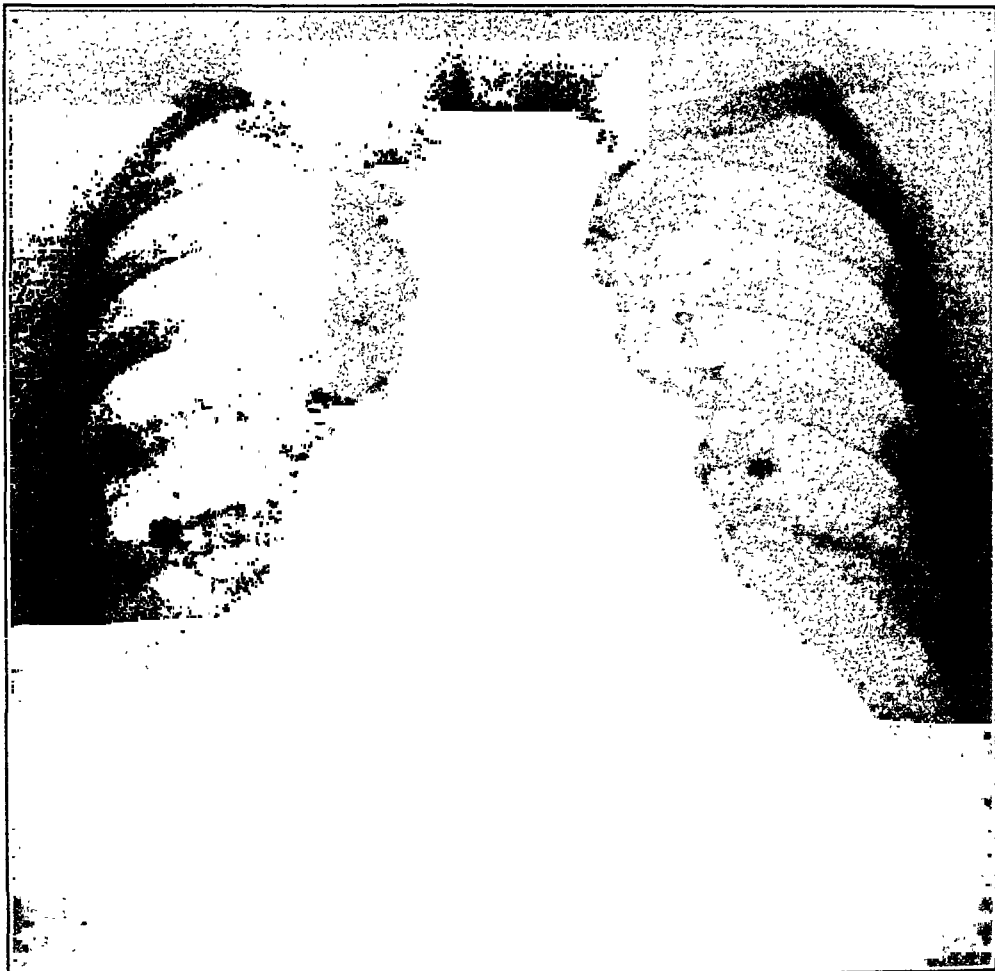


Fig. 1.—Roentgenogram taken September, 1929. Note the generalized enlargement of the cardiac shadow, and particularly of the pulmonary conus.

Roentgenograms of the chest showed the heart shape characteristic of mitral valvular disease. The electrocardiogram showed bundle-branch block. Kidney function was normal.

The patient was discharged April 14, 1930, in an improved condition.

During the summer, while under observation in the out-patient department, she developed auricular fibrillation. This, however, caused no change in her condition, as she was well digitalized.

*Third Admission.*—She returned to the hospital for the third time on Oct. 11, 1930. She had been fairly comfortable until three days prior to admission when



A roentgenogram of the chest (Fig. 2) revealed a mitral heart configuration, with marked enlargement of the pulmonary conus. The blood pressure readings were as follows: left upper extremity, 200/124; left lower, 202/134; right upper, 176/118; right; right lower, 192/134.

The patient did not improve with digitalis and the theobromine preparations. She complained constantly of pain over the liver. She died suddenly on Dec. 3, 1930.

The diagnosis considered most likely was mitral stenosis with aortic insufficiency. The basal diastolic murmur was louder and more constant and had a wider propagation than the usual Graham Steell murmur. This suggested the origin of the murmur in the aortic valve rather than in the pulmonic. Furthermore, the patient's pulse pressure was so high (60 to 110 mm.) that a Corrigan pulse was present. In retrospect we realize that we should have been impressed by the enlargement of the pulmonary conus and the negative Hill's sign.<sup>81</sup>

### *Post-Mortem Findings*

The post-mortem examination was made by Dr. Alfred Plaut, to whom I am indebted for the pathological report. The body was that of a middle-aged white woman of medium height who was fairly well nourished. The heart findings only are given in detail.

The heart weighed 575 gm. and measured 11 by 10 by 6 cm. The apex was formed by the left ventricle. The left edge of the heart was very much rounded. The right ventricle was not as hard as the left but still was fairly well contracted. The mitral and tricuspid ostia were normal in width. The left ventricle was wide, but not in relation to the thickness of its wall. The anterior wall reached a thickness of about 3 cm. The papillary muscles were thick and slightly flattened. The trabeculae were more flattened than the papillary muscles. The upper half of the anterior portion of the septum was thinned out in a circular area nearly 4 cm. in diameter. The inner posterior margin of this area came fairly close to the location of the bundle of His. This margin was vertically below the commissure between the right and posterior aortic cusp. The lower margin of the area of myomalacia was situated at the origin of the posterior capillary muscle, while its uppermost end nearly touched the septum membranaceum. The area surrounding the coronary vein on the right side of the septum atriorum was intact as was the lower edge of the septum membranaceum. The tissue of the septum outside the area of myomalacia appeared intact. In this circular area, which lay a few millimeters below the level of the surrounding endocardium, the color gradually changed from reddish brown to purplish yellow. The wall in the center of this area was thinned out to about 4 mm. Directly under the endocardium there were yellow streaks which corresponded to the yellow areas seen from the inside. The mitral and aortic valves appeared normal except for small thickenings. The commissures were not widened. The aortic ostium, after opening, measured 6 cm. The tricuspid valve was intact. The pulmonary ostium, after opening, was a little over 7 cm. wide. The pulmonary valve, notably the anterior cusp, stretched considerably when the ostium was opened. The pulmonary artery was very inelastic, notably in comparison with the rather elastic aorta. A few small yellow spots were visible in the intima over the attachment of the ligamentum arteriosum. Otherwise the pulmonary artery appeared intact.

There was an extra commissure between the right and the anterior cusp, making an abortive supernumerary cusp, 4 mm. wide (Figs. 3 and 4). The commissures were nearly equal in length and created a fold on the inside of the pulmonary valve when the valve was pulled downward. They differed in thickness, the left one being considerably thicker than the right. Only the right commissure united

the upper edge of the valve with the pulmonary artery and with the edge of the neighboring cusp. The thicker commissure united the anterior cusp to the pulmonary artery and was attached nearly 2 mm. below the free margin of the valve.

The right ventricle was considerably narrowed by the bulging of the hypertrophic septum. The papillary muscles were slightly thickened. The trabeculae appeared more hypertrophic, notably over the septum. They were not flattened to any marked degree. The anterior wall without trabeculae had an average thickness of 3 mm. The myocardium was very firm throughout with the exception of the above mentioned area of myomalacia. It was very shiny, pale pink, homogeneous, with very indistinct markings on the cut surface. The upper half of the left posterior papillary muscle contained gray and yellowish spots. Long section through the left anterior papillary muscle revealed extensive scar formation. The subepicardial fat, which was fairly thick, was well separated from the myocardium. The ascending aorta as elastic and thin, and there was much atheroma but no sclerosis. The left coronary artery was normal in width but was atheromatous. The wall was not hardened and the lumen not narrowed. Behind the left edge,

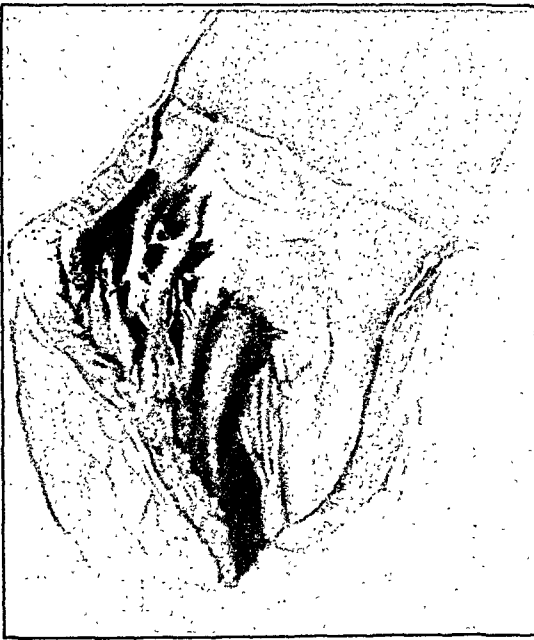


Fig. 3.



Fig. 4.

Fig. 3.—A dimple is visible at the site of attachment of the supernumerary commissure. The supernumerary cusp is left of this commissure. This illustrates the case with which the anomaly may be overlooked.

Fig. 4.—The abortive supernumerary cusp lies between the anterior cusp, which has been pulled down, and the right cusp.

however, thick, firm, yellow masses narrowed the lumen and occluded it completely 5 cm. from the aorta for a distance of about 0.5 cm. Below the occlusion the lumen was fairly normal and the wall of the artery thin. The ramus descendens anterior was considerably atheromatous down to the middle of the left ventricle, where the wall became normal. The right coronary artery was normal in width nearly up to the right edge, although many yellow deposits were found in the intima. Directly behind the right edge, the lumen was occluded for a distance of 5 cm. by an adherent red thrombus. The thrombus was situated in a moderately narrowed vessel with considerable atheromatosis. Beyond the thrombosis the lumen was slightly narrower than the normal. There was considerable atheromatosis of the horizontal branch, while a branch going down toward the apex appeared fairly normal except for its beginning. The myomalacious spot was situated directly below the point of occlusion.

The aortic arch was moderately arteriosclerotic. The thoracic aorta was elastic, with considerable atheromatosis. Its average width was 5 cm.

*Microscopic Examination.*—In the thin portions of the pulmonary valve, including the normal commissure, only minor changes could be detected. There were, for instance, small accumulations of round and elongated nuclei in the endocardium. Not far from the free edge of the valve there was an oblong area where the tissue was very loose, did not stain with eosin, and contained a relatively large number of round, large nuclei. There were larger areas in the thin valve which appeared homogeneous and contained very few nuclei. The neighboring myocardium contained many small scars.

In the normal commissure there were accumulations of round cells in the loose tissue between the pulmonary valve and the aorta. The pulmonary valve appeared intact. The aortic valve was thickened and the nodule calcified. The wall of the heart below the abnormal commissure contained nothing unusual. In the sections from the abnormal commissures, no inflammation was found. There were, however, some cellular aggregations in the pericardial fat.

*Diagnosis.*—Hypertrophy of the heart. Sclerosis of the coronary arteries, notably of the left circumflex branch. Recent thrombosis of right circumflex branch. Circumscribed myomalacia in outer and upper part of left ventricle. Abortive supernumerary cusp (congenital) of the pulmonary valve. General arteriosclerosis. Swelling of spleen. Swelling and fatty change in liver. Healed tuberculous focus in middle lobe of right lung. Submucous hemorrhages in small intestine. Submucous nodule in duodenum (aberrant pancreas). Myomata uteri.

#### DISCUSSION

The patient had essential hypertension which became "malignant." Sclerosis of the coronary vessels resulted in myocardial weakening and circulatory failure. Death came when the sclerotic coronary vessels became thrombosed. The only valvular lesion of the heart was the supernumerary cusp in the pulmonary valve. The apical systolic murmur was either functional in origin or was transmitted from the pulmonary valve. The apical diastolic sound was probably the third heart sound of gallop rhythm. The basal diastolic murmur and the enlargement of the pulmonary conus observed in the roentgenograms were caused by pulmonary insufficiency. The generalized enlargement of the heart shadow was due to hypertrophy and dilatation of the heart.

An important question must be answered. Did the presence of the supernumerary cusp in the pulmonary valve render the valve incompetent or was the cusp an adventitious finding? Longworth<sup>82</sup> in 1878 demonstrated that the optimum number of semilunar cusps is three. For maximum efficiency of the pulmonary valve, the cusps during systole should lie flat against the arterial wall whereas during diastole the segments should fall together and come in contact with each other as far as the center of the artery. To fulfil these two conditions the combined length of the free borders of all the cusps must equal the circumference of the artery and the length of each free border must equal twice the radius of the artery. Only if there are three cusps will both

conditions be fulfilled, inasmuch as three diameters (or more exactly  $\pi$  or 3.1416) equal the circumference. Two, four, five, or any other number of valvular segments can fulfil only one of the two conditions. (Fig. 5.) It may be said, therefore, that in the case here presented, the pulmonary valve did not operate at maximum efficiency.

At necropsy the pulmonary valve did not appear unquestionably incompetent, but during life it most probably was. Normally, the pulmonary ring is more distensible than the aortic ring (Gibson<sup>80</sup>), and it is likely in this case, since an inelastic pulmonary artery was found post mortem, that the pulmonic ring was stretched during life. The valvular anomaly probably permitted at the pulmonary orifice a slight degree of regurgitation which was negligible for many years until left ventricular failure developed and the pressure in the pulmonary circuit rose. As the pressure rose, the valve became increasingly incompetent.

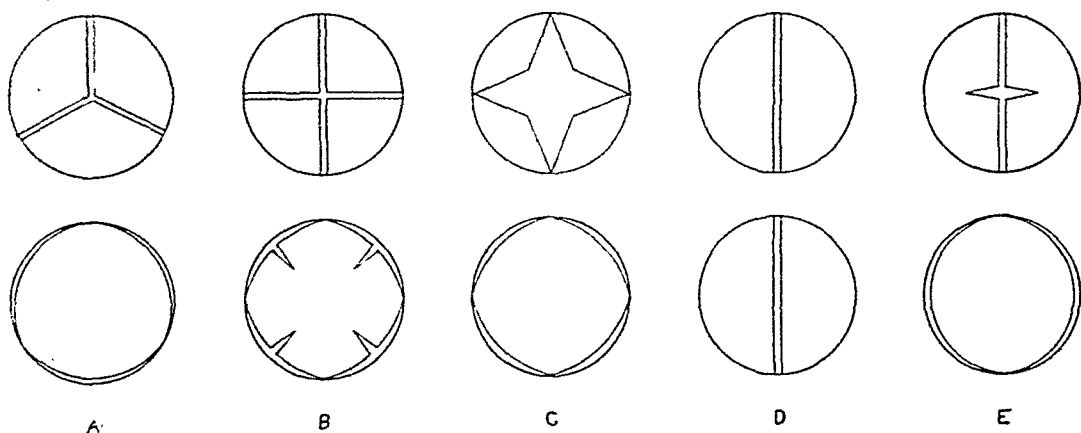


Fig. 5.—Influence of the number of cusps on efficiency of semilunar valve. Upper row, valve closed, lower row, valve open.

A, three cusps, efficient closure, efficient opening. Length of free border of each cusp equals two radii or one diameter. Combined lengths of free borders equal six radii or three diameters. Circumference also equals three diameters or more exactly,  $3.1416 \times$  diameter. When valve is closed, cusps are just long enough to meet in center without overlapping. When open, free borders fit closely against arterial wall without overlapping.

B, four cusps, efficient closure, inefficient opening. Combined length of free borders equals eight radii or four diameters. When valve is open, there is excess length of one diameter (more exactly, six-sevenths diameter) so that cusp borders overlap.

C, four cusps, inefficient closure, efficient opening. Combined length of cusps equals three diameters. Each cusp's length is only three-fourths diameter and cannot close up to center of artery.

D, two cusps, efficient closure, inefficient opening. Combined length of free borders equals two diameters. Cusps cannot move and valve cannot open.

E, two cusps, inefficient closure, efficient opening. Combined length of free borders equals three diameters. Each cusp's length is one and one-half diameters, an excess of one-half diameter for each cusp when valve is closed.

With beginning failure, while the pulmonary arterial pressure was still low, the degree of regurgitation was slight. During the last month of life, the murmur of pulmonary insufficiency became louder and louder because the degree of regurgitation increased. The left ventricle failed progressively, the pressure in the pulmonary circuit rose higher and higher, and the valvular ring dilated increasingly. At first,



while the circulation was still competent, the roentgenograms disclosed no enlargement of the pulmonary conus. Later, the pulmonary conus showed a moderate degree of dilatation. Still later, when the murmur was loudest and the regurgitation greatest, the conus was largest.

#### CRITERIA FOR DIAGNOSIS

The appreciation of a condition often leads to its recognition. The next case, it is hoped, will not be overlooked. In Pitt's series<sup>84</sup> of cases of pulmonary insufficiency assembled from the literature and from the records of Guy's Hospital, there were sixteen cases of pulmonary insufficiency associated with an abnormality in the number of pulmonary cusps. In six cases there were four cusps, in nine cases two cusps, and in one case five cusps.

It is clear from a study of the literature that four cusps in the pulmonary valve may occur without symptoms or signs of pulmonary insufficiency. It is quite likely that many of the cases reported as lacking signs were not examined for a diastolic murmur in the pulmonary area. In other cases, it is possible that regurgitation and a diastolic murmur were not present, although the valve was incompetent anatomically, because the pulmonary arterial pressure was lower than the right ventricular pressure.<sup>84</sup> At any rate, those cases which lack clinical evidence of the anomaly can be discovered only post mortem.

But there are cases with clinical manifestations of pulmonary insufficiency. In cases of pulmonary insufficiency, in the absence of another cause, such as bacterial endocarditis or mitral stenosis, a congenital anomaly, such as four cusps, or two cusps in the valve, may be suspected. Pulmonary insufficiency must be considered when a diastolic murmur is heard at the base of the heart in the absence of the peripheral signs of aortic insufficiency. When marked enlargement of the pulmonary conus is observed in the roentgenogram (Schwartz<sup>86</sup>), pulmonic incompetence is suggested. Fluoroscopic findings are often characteristic. There occurs a pulsation of the pulmonary artery—"the dance of the hiluses"<sup>83</sup>—comparable to the dynamic aorta seen in aortic insufficiency.

Pulmonary insufficiency is accompanied by hypertrophy and dilatation of the right ventricle and right auricle and often of the pulmonary artery itself. The tricuspid valve may become incompetent, with the evidence of a large pulsating liver and jugular reflux. Dyspnea may be extreme and disproportionate (Sansom<sup>85</sup>).

#### SUMMARY

1. A case of pulmonary insufficiency is described in which a loud diastolic murmur was heard at the base of the heart and in which four cusps in the valve were found at necropsy.

2. Review of the literature reveals that a supernumerary pulmonary cusp may occur without signs or symptoms. The anomaly may be associated, as in the case here presented, with pulmonary regurgitation.

3. The diagnosis has never been made ante mortem.

4. Three semilunar cusps are the optimal number. If there are four cusps (or two or five), the pulmonary valve cannot operate at maximum efficiency (Longworth<sup>82</sup>).

5. There are cases in which unexplained basal diastolic murmurs are present with no evidence of aortic insufficiency. It is suggested that some of these are due to an anomaly of the pulmonary valve.

\* \* \* \* \*

I wish to acknowledge my indebtedness to the late Dr. Marcus A. Rothschild for his aid.

#### SUMMARY OF CASES OF FOUR PULMONARY CUSPS

1. a.<sup>+</sup> 13.181<sup>1</sup> Ref.: R.V.H. 21/98. Female, aged fifty-six years, who died of chronic nephritis and arteriosclerosis. Posterior segment little larger than others and sinus behind it is divided into unequal parts by delicate raphe 5 mm. from left corner. Raphe is half height of sinus.

b. 13.181<sup>2</sup> Ref.: 3959 F. 255/08. Male, three and one-half months old, who died of inanition. Heart small size and atrophic. Ductus arteriosus patent. Three cusps larger and of equal size; fourth narrower, about one-half width of others, fenestrated and dipped a little deeper into the heart musculature. Between left and right posterior cusps.

c. 13.181<sup>3</sup> Ref.: E. 7892 M.G.H. 192/22. Female, aged thirty-nine years. No cardiac symptoms. Died following operation for right hydronephrosis. Heart normal size. Tricuspid valve slightly abnormal—septal and infundibular cusps inserted directly into pars membranacea, leaving 6 mm. interval between them. Left auricle much smaller than right. Left ventricle hypertrophied. Mitral valve sclerotic. Right auricle capacious but not hypertrophied. Pulmonary artery larger than aorta, 7.2 cm. diameter. Cusps well formed, delicate fenestrated. Three segments equal, 2 cm. wide, fourth, 1.4 cm. Between anterior and right posterior cusps.

2. a. Male, aged thirty-six years, who died of a "compound heart defect." Dilated and hypertrophied heart. Incompetent aortic valve. Dilatation, ulceration, and atheroma of aorta. One cusp smaller than other three. Small cusp on posterior wall between right and left cusps. Larger cusps 3 cm. across, small cusp 2 cm. Large cusps 17 mm. deep, small one 7 mm. Large cusps semilunar shaped, small cusp funnel shaped, broader below. Each cusp possessed a corpus Arantii.

b. Female, forty-two years old, who died of pulmonary edema. Mitral stenosis. Hypertrophied and dilated heart. One of cusps small. All four fenestrated and had thickened corpora Arantii. Larger cusps 2.5 cm. across, smaller 1.5 cm. Depth of larger cusps 1.5 cm., of small 1.2 cm. Small cusp between anterior and right cusp. Small cusp a little swelled out below.

c. Male, twelve years old, who died of miliary tuberculosis. Two cusps half as large as other two. Larger ones each 2 cm. wide, smaller 1 cm. Depth of larger cusps 1.5 cm., of smaller 1 cm. One anterior cusp, one right, and two left (the smaller). Two smaller cusps partly fused together and attached to arterial wall only above and below. Each cusp possessed a corpus Arantii.

3. Picture of valve with four cusps, all fenestrated.

\*The numbers correspond to the reference numbers.

4. Male, aged twenty-one years. Dyspnea on exertion. Systolic and diastolic basal murmurs. Right arm smaller than left from birth. Died of a fractured skull. Pulmonary valve slightly incompetent to water. Three cusps of ordinary size, fourth much smaller and imperfectly separated from one of other cusps.

5. Male, fifty-four years old. Nocturnal asthma and palpitation. Systolic and diastolic thrill. Systolic apical murmur. Diastolic murmur heard best in fourth left interspace. Died of "collapse" of the heart. Resolving lobar pneumonia. Hypertrophy of all heart cavities. Aortic valve and aorta atheromatous. Mitral cusps retracted. Pulmonary artery aneurysmal, circumference 3 cm. from origin measured 160 mm. Three cusps of equal and normal size, fourth smaller. Difference in size limited only to width; height and thickness equal to that of other three. Valve sufficient.

6. Male, aged fifty-seven years, who died of tuberculosis. Two anterior valvules larger. Two posterior valvules one-half less than others in size. All cusps reticulated. Right anterior cusp 21 mm. wide by 20 mm. deep, left anterior 21 by 26 mm., right posterior 14 by 15 mm., left posterior 13 by 13 mm.

7. Two cusps of equal size, third smaller, fourth very small, rudimentary, but perfectly formed with a corpus Arantii.

8. Case 4. Three cusps of equal size, 2 to 2.5 cm. wide, 2 cm. deep. Fourth cusp half as large, 1.2 cm. wide and 1.5 cm. deep.

Case 5. Moderate hypertrophy of left ventricle. Thickening, calcification, and insufficiency of mitral valve. Aortic valve thickened. Patent foramen ovale (size of lead pencil). Three cusps of same size, 1.5 to 2 cm. wide, fourth smaller, lying between right and anterior cusp. Free margin 0.7 cm. wide. From free margin to floor of pocket 1 cm.

Case 6. Right ventricular musculature relatively thick. Patent foramen ovale (size of lead pencil). Three cusps of equal size, 2 to 2.5 cm. wide, 1.5 to 2 cm. deep. Fourth cusp between anterior and left cusps; 0.3 cm. wide at top but increasing in width toward lower border, forming a narrow-mouthed pocket. All cusps adherent at tips. Insufficiency of valve.

9. No cardiac symptoms or signs. Death from tuberculosis. Fourth cusp between internal and posterior cusps. Like others except in size. After alcohol fixation, 10 mm. across, the others 24, 19, and 18 mm.

10. a. Female, aged thirty-six years. Patient epileptic. No cardiac symptoms or signs. Diffuse acute periencephalitis, atrophy of brain, acute croupous pneumonia, hyperemia of abdominal organs, atheroma of aorta. Three cusps equally large, 1.5 cm. wide, fourth one-half the size. All cusps fenestrated along free margin, small cusp more than others.

b. Male, sixty-four years old. In his last years suffered from shortness of breath on the slightest exertion. No physical examination of the chest before death. Large heart. Left ventricle dilated, walls thickened. Right ventricle enormously dilated, wall greatly thickened. Aorta atheromatous. Atrophy and edema of brain, edema of lungs, hyperemia of spleen and kidneys. Three cusps about same size and shape (2 cm. wide), fourth half that size. All cusps fenestrated, fourth more than others.

11. Male adult. No cardiac signs. Died from gangrene of the lung. Fourth cusp between right anterior and posterior segments, similar to others in shape but much smaller. Depth one-third that of others, breadth one-fifth that of others. No corpus Arantii. Sinus communicated with sinuses of neighboring cusps. Valve competent.

12. Male, sixteen months old, who died of bronchopneumonia. Supernumerary cusp situated a little below level of attachment of other cusps. Distinct corpus Arantii.

13. Description of case not available.

14. Male, eighty years old. Occasional attacks of weakness. Mitral regurgitant murmur. Aortic sounds double. No definite history of a tricuspid murmur. Heart enlarged, weighed 27 ounces filled with blood. Aortic valve incompetent to water. Walls of right ventricle thin. Pulmonary artery enlarged. Valve incompetent to water. Circumference of artery just above valve, 9 cm.; broadest portion of artery just before bifurcation, forming a pouch 14 to 16 cm. in circumference. Four perfect cusps.

15. a. Three of curtains well formed, but there was an additional sigmoid pouch capable of holding a pea.

b. Septum between two of the cusps longer than others.

c. Very minute, imperfectly formed additional cusp formed by a little curtain supported above by slender cords.

d. Still more minute extra cusp not only attached laterally to the artery by tendinous cords, but also presenting a thin membranous bridle which extended upward from that portion of the free edge at which the corpus Arantii is usually situated to the arterial wall above.

e. Four perfectly formed symmetrical leaflets.

16. Fourth cusp about one-third size of normal cusp and situated between two posterior cusps.

17. Male, thirty-two years old. No cardiac symptoms or signs during last illness. Death from acute nephritis complicated by pleuritis and compression of the lung. Three cusps of equal size; fourth, one-half width of others, situated between anterior and posterior cusps. Two adjacent cusps fenestrated. Rudimentary fourth cusp filled in defects of other two cusps. Fourth cusp shorter than others and lay on a lower level. Margin held in place by two long thin fibrous strands stretching from near its center to angles of attachment of two adjacent cusps.

18. a. Male, four years old, who died of postdiphtheritic myocarditis and sero-fibrinous pleurisy of left lung. Each cusp about 9 to 10 mm. across and 8 to 9 mm. high. In all respects normal. Small fenestration on each cusp.

b. Female, seventy-eight years old, who died of bilateral bronchopneumonia with left fibrinous pleurisy. Left anterior cusp 18 mm. wide and 18 mm. deep; right anterior 20 by 16; right posterior 14 by 12; left posterior 14 by 12. Two posterior cusps fenestrated at angle of insertion.

c. Female, twenty-seven years old, who died of miliary tuberculosis. Hypoplastic heart and aorta. Three cusps of equal size and larger than fourth as follows: 15 mm. wide and 13 mm. deep; 16 by 12; 15 by 12; 6 by 5. Cusps of uniform thickness throughout, there being no thinning along lunula and no corpora Arantii. Fourth cusp fenestrated.

d. Male, nine years old. Faucial diphtheria. Bilateral bronchopneumonia. Three cusps of approximately equal size: one 14 mm. wide and 12 mm. deep, second 15 by 12, third 14 by 11. Fourth smaller, 8 by 7 mm. and on a lower plane than the others.

e. Male, forty-eight years old. Adherent pericardium, enlarged heart, particularly left ventricle and left auricle. Aortic stenosis and insufficiency. Dilated right ventricle. Pulmonary edema, chronic passive congestion of splanchnic viscera. Anterior cusps larger and equal: left anterior 18 by 14 mm., right anterior 19 by 14; posterior cusps smaller and almost equal: right 14 by 14, left 15 by 13. Left anterior fenestrated.

19. Male, forty-eight years old. Normal heart rhythm. No murmurs. Died of uremia. Small sclerotic kidneys. Emphysema and chronic bronchitis. Left ventricle hypertrophied. Aortic valve sclerotic and thickened. An anterior, a posterior cusp, a

right and left lateral. Posterior 25 mm. wide and 10 mm. deep, anterior 21 by 11 and had a corpus Arantii, left 25 by 19. Posterior valvule like Bernard's case. Pulmonary orifice 97 mm. in circumference.

20. a. Adult. Diffuse atheroma at beginning of aorta and mitral and aortic valves. Patent foramen ovale but with a sufficient valve. Three cusps larger, 18, 20, 22 mm. wide and 13 to 15 mm. deep; fourth, between posterior and right, 8 mm. wide and 10 mm. deep.

b. Adult. In right auricle at site of foramen ovale, an invagination 5 mm. deep but not communicating with left auricle. Three cusps 18 to 20 mm. wide and 13 to 17 mm. deep. Supernumerary cusp between posterior and left; 10 mm. wide and 12 mm. deep.

c. Adult. Supernumerary cusp between posterior and right cusps, 12 mm. wide. Other three, 20 to 23 mm. wide and 15 mm. deep.

d. Adult. Width of cusps, 13, 17, 18, and 25 mm., respectively. All 15 mm. deep. Supernumerary cusp between right and left.

21. a. Male, sixty years old. Tuberculosis of osseous system. Fourth cusp between left and anterior cusp, small.

b. Male, fourteen years old. Fourth cusp between right and left cusps, small.

c. Male, sixty-two years. Two cusps a bit larger than the other two which were somewhat grown together.

d. Small cusp between right and left cusps.

e. (No data on other five cases.)

22. a. Male, one year old. Atelectasis of lungs, intestinal catarrh, and rickets. Fourth cusp smaller. Communicated with neighboring cusps. Dilatation of pulmonary artery and right ventricle.

b. Male, fifty-two years old. Chronic pneumonia, miliary tuberculosis and vertebral caries. Fourth cusp very small and fenestrated.

23. Male, old. Extra cusp 1 mm. less in height than other three but otherwise just like them.

24. Male, thirty-one years old. Died from hemorrhagic apoplexy. Slight atheroma of aortic arch. Fourth cusp somewhat smaller than its fellows and communicated with one of them at its insertion by an aperture large enough to admit a crow quill. No corpus Arantii.

25. No heart disease. Supernumerary cusp much smaller than others but presented same configuration.

26. Male, fifty years old. Died from phthisis. Heart normal. Each of cusps well formed and possessing corpus Arantii. Three equal sized, fourth scarcely half breadth of others.

27. Male, who died of typhus fever. Incompetency of tricuspid valve diagnosed during life. Three cusps about same size, fourth considerably smaller than others and with an inconspicuous corpus Arantii. All four cusps fenestrated. Fenestrations larger in small cusp.

28. Large heart. Right ventricle somewhat dilated. Patent foramen ovale (2 cm. diameter). Rudimentary supernumerary aortic cusp. Diameter pulmonary artery 9.3 cm. Width of anterior and left posterior cusp, each 3 cm. Right posterior, 2.5 cm. wide and 1.5 cm. deep.

29. Patient died of typhoid fever. During life there was heard a murmur which replaced the first sound and lasted until almost the beginning of the second. Four valvules in pulmonary artery, of normal shape.

30. See Reference Number 4.

31. Well marked presystolic murmur. Case with four pulmonary cusps similar to Coleman's.<sup>16</sup>

32. Two cases with four pulmonary cusps.

33. Manuscript not available. (Reference not checked.)

34. Female, old. Circumference of pulmonary artery  $3\frac{1}{8}$  inches. Three of cusps measured 1 inch wide, fourth  $\frac{1}{8}$  inch. Supplementary cusp resembled others except in size. Corpus Arantii present. Fourth cusp reticulated.

35. a. Male, nineteen years old, who died of cancer and tuberculosis of the lung. Two valvules of equal and normal size and appearance and one large valvule, attached border of which was imperfectly doubly crescentic. A little to one side of center of free border of cusp was a single very large corpus Arantii. From this body a septum proceeded dividing the cusp in two compartments.

b. Heart identical anatomically with above.

c. Three valvules of nearly equal size. Between two of these, a fourth smaller cusp with its own corpus Arantii.

36. All three patients died of disease not related to the anomaly.

a. Three larger cusps and one smaller. Supernumerary cusp between anterior and right lateral cusps was half the width and half the depth of other three cusps. No nodule of Morgagni. Tendinous cords from lateral margins of cusp to arterial wall. All cusps but one fenestrated.

b. Supernumerary cusp half height and width of other three. Situated between anterior and left lateral cusps. No nodule of Morgagni. Intravalvular pocket at its base. All cusps communicated with one another. Fibrinous cords at commissures. Fenestration of cusps at commissures.

c. Two normal-sized cusps and two half their depth and width. Two smaller cusps equal in size. They replaced right lateral cusp. Many fenestrations. Communication between smaller cusps below and larger ones above.

37. In six cases, the right septal cusp was subdivided, the left also in six, so that in each of twelve cases there were four cusps.

38. Female, sixty years old, who died of ruptured aneurysm of iliac artery. Always sickly. Systolic apical murmur. Accentuated second pulmonic second sound. Thyroid enlarged. Heart enlarged, especially right auricle. Thickening of mitral valve, no narrowing. Stiffening of aortic valve but no insufficiency. Dilatation of pulmonary conus. Small fourth cusp between right and left cusps, its free border being at level of lower surface of neighboring cusps. Two bands of tissue ran from middle of its free border to sinus border.

39. Female, thirty-four years old. Suffered from palpitation of the heart, pain in the chest and difficulty in breathing. Cyanosis, intense dyspnea, ascites, edema of lower extremities. Systolic and diastolic murmurs over pulmonary area. Heart enlarged. Right auricle dilated. Patent foramen ovale. Right ventricle enormously dilated, trabeculae hypertrophic. General anasarca. Pleural effusion. Purulent bronchitis. Congestion of liver, spleen, and kidneys. Conus arteriosus very wide, likewise pulmonary artery. Right and left posterior, and right and left anterior cusps. Left posterior cusp very small, free border about 4 "linien"\* wide. Other cusps each 6 to 8 "linien" wide.

40. Male, fifteen years old. Signs of mitral and aortic insufficiency and of pulmonary tuberculosis. Acute pericarditis, mitral and aortic insufficiency. Pulmonary tuberculosis. Two cusps larger, two smaller.

41. Male, six years old. Systolic thrill over precordium. Systolic murmur along left border of sternum heard best between third and fourth ribs. Second pulmonic sound greatly accentuated. Slight dilatation and hypertrophy of heart. Aneurysm and endocarditis of aortic valve. Patent interventricular septum and foramen ovale. Bronchopneumonia. Three cusps each 1.5 cm. wide, fourth 3 mm. wide.

42. One cusp much smaller than the other three.

\*One "Linie" = 2.195 mm.

43. Male, sixty-one years old. Palpitation and dyspnea on effort. Pulse rate 27, bigeminal. Systolic basal murmur in pulmonary area. Emphysema. Cyanotic. Heart weight 520 gm. Wall of left ventricle hypertrophied. Aortic valve slightly indurated but otherwise normal. Right auricle and ventricle thin and diminished in size. One cusp, left and a little anterior, 1.9 cm. wide and 1.7 deep, with corpus Arantii. Second, anterior and a little to right, 1.4 by 1.6 cm., shrivelled and plaited, with no nodule. Third, posterior and right, 2 by 1.8 cm. Fourth, posterior and left, 2.5 by 2.1 cm., with vestige of corpus Arantii.

44. a. History not obtained. Pulmonary artery quite wide. Four well-built cusps. Anterior and right cusp each 2 cm. wide, other two 1.5 cm. across. All had corpora Arantii. Upon right cusp, a sinewy thickening, 2 to 3 mm. wide, parallel to upper border. Similar thickening below nodule of left cusp. This cusp had a small fenestra. Fourth cusp free of defects but had marked fibrous thickening along free border.

b. History not obtained. Heart atrophied. Muscle fatty. Wall of right ventricle thin. Patency of intra-auricular septum. Three cusps normally built, fourth rudimentary, between posterior cusps. Three larger each 20 mm. wide, smaller 8 mm. Large cusps 17 to 20 mm. deep, small one 6 mm. Free border of latter ran upward and to right in a thin fibrous cord leaving a space about the size of a millet seed between itself and the cusp.

45. a. Female, sixteen years old, who died of chronic nephritis. Two cusps of equal size and normal. Between these two were two others, a little larger, of equal size, possessing rudimentary corpora Arantii.

b. Male, forty-four years old, who died of pulmonary tuberculosis. One cusp 22 mm. wide by 18 mm. deep, well formed and with corpus Arantii. Second, 25 by 21 mm., without corpus Arantii. Between two preceding cusps, two others fused together, larger of which was 24 by 19 mm., smaller 14 by 13 mm. Along free margin was a fibrous cord attached obliquely to arterial wall and which inserted above smaller cusp. Another rudimentary lower cord. Smaller cusp fenestrated.

46. All cases past puberty. No subjective symptoms or signs related to the anomalies in any case.

*Case V.* Heart enlarged. Right auricle larger than normal. Right ventricle much larger than left. Heart infiltrated with fat subpericardially. Two larger cusps, anterior, two smaller, posterior. All cusps had nodule of Morgagni.

*Case VI.* Right ventricle thin. First cusp, 15 mm. wide by 10 deep. Second, 20 by 14 mm., free border curved, convexity upward. Third, 13 by 9 mm. Fourth, supernumerary cusp, placed in angle formed by insertion of two adjacent cusps. Valve not attached directly to arterial wall but to adjoining valvules. Four very fine bands of tissue running from free border, inserting in space between points of insertion of free borders of adjacent cusps. Length of free border of supernumerary cusp 4 mm., height 3 mm. All cusps lacked nodule of Morgagni.

*Case VII.* Heart larger than normal, left side more than right. Slight thickening of mitral valve. Three cusps of equal size and normal. Fourth not as deep as others nor as high. Two bands running from fourth cusp to arterial wall. Height of fourth cusp 8 mm., width 10 mm., others 16 by 28 mm.

47. In his (Meckel's) father's collection were four cases of hearts with four pulmonary cusps. First case showed a single large cusp and other three equal but much smaller. Second and third cases, one very large cusp, two a little smaller, the fourth much smaller than usual. Fourth case showed three cusps of equal size and normal; fourth cusp was very small; scattered small fenestrae in all cusps, and none had nodule of Morgagni.

48. Five cases noted, including the four cases given as under No. 17. One, three cusps lacked a little of the usual size, but the fourth was very small (discovered by

Meckel, senior). Two, two cusps a bit smaller but equal, third of normal size, fourth smallest (discovered by Meckel, senior). Three and four, the son had two more cases almost exactly like second case. Five, no two cusps equal, but sizes decreased in order.

49. a. Female, eighty-five years old. Four cusps of equal size. Extra cusp between right and left. Left and supernumerary cusps joined together at commissure. Right cusp projected 3 mm. above level of other cusps. Corpora Arantii all well developed. Patent interventricular septum.

b. Male, eighty-three years old. Extra cusp between right and left, smaller than its neighbors. Free border 8 mm. All four cusps fenestrated. Patent interventricular septum.

50. Three cases seen. In one, all cusps were of approximately equal size.

51. Female, thirty-nine years old, who died of intestinal obstruction due to strangulated femoral hernia. No disorder related to the circulation. Peritonitis. One cusp larger than others, anterior and to left of others.

52. No features of special interest among symptoms and signs. Cusps well formed, measuring 2, 1.8, 1.8, and 1.4 cm. respectively, along free border. Largest one a little thickened. All fenestrated.

53. a. No clinical manifestations. Supernumerary cusp 8 mm. wide and 8 mm. deep. No corpus Arantii. Anchored to wall of artery by small narrow tag. Lateral attachments to adjacent cusps, not artery. Two or three fenestrations of large cusps communicated directly with fenestrations of small cusp. Three larger cusps of equal size and normal.

b. Small supernumerary cusp 7 mm. wide and 8 mm. deep. Lateral edges united to contiguous cusps. Sinus distinct and did not communicate with adjacent sinuses. Adjacent cusps smaller than third.

54. Eight cases.

55. Male, forty-six years old, who died of chronic phthisis, with genitourinary complications. Heart somewhat increased in size and weight (9 ounces and 14 drams). Cavities of large size and walls moderately thickened. Two smaller cusps formed by division of one larger cusp.

56. First cusp to right, second and third toward center posterior, fourth left. Third cusp much smaller than others, finer in structure and reticulated. Each cusp had corpus Arantii placed in center.

57. Double ascending aorta. Three cusps larger, fourth very small.

58. a. Four cusps, 10, 20, 21.5, and 20 mm. in width.

b. Four cusps, 17, 9, 20, and 15 mm. in width.

c. Hypertrophy of left ventricle. Aortic insufficiency and stenosis. Four cusps, 23, 14, 13, and 18 mm. in width.

d. Much calcification of aorta. Hypertrophy of left ventricle. Four cusps, 17, 25, 15, and 6 mm. in width.

e. Author mentioned two more cases but gave no data.

59. Female, thirty-one years old. On eleventh day after cholecystectomy, sudden distress developed with marked dyspnea, cyanosis, and rapid pulse. Severe right heart dilatation with bulging of auricle and venae cavae. Weight 290 gm. Myocardium flabby, with slight fatty infiltration particularly in right ventricle. Slight thickening of mitral and aortic valve leaflets. Fourth cusp small and appeared to be derived from anlage of left posterior cusp. Small cusp fenestrated and had no corpus Arantii.

60. Male, seventeen years old. Four well-shaped leaflets, 13, 17, 14, and 16 mm. in width. Two middle leaflets at line of junction joined to arterial wall by wedge-shaped bridge of fibrous tissue which acted as a partition and divided the whole cusp in two. Partition perforated near top. Only first, second, and fourth cusps had corpus Arantii, third had only small condensation near middle.



61. *Case VII.* Female, old. No symptoms. Died of enteroperitonitis. Three of cusps each 15 mm. wide, fourth 18 mm.

*Case VIII.* Male, fifty-five years old. Abscess of leg. Empyema. Two of cusps 15 mm. wide, third 13 mm., fourth 8 mm. In each of the two larger ones, rather than a corpus Arantii was an enlargement of median part of free border. Other two cusps, no trace of corpus Arantii.

*Case IX.* Male, fifty years old. Heart larger than normal through marked hypertrophy of left ventricle and auricle. Thickening of endocardium of mitral valve by a mild chronic endocarditis. Aortic valve, insufficient and stenosed. One cusp 19 mm. wide and 10 high, second 13 by 10 mm., third 14 by 14 mm., fourth 16 by 15 mm.

62. Cusps intact. Supernumerary cusp one-half size of others.

63. Male, fifty-seven years old. No clinical history. Sudden death. Left ventricle hypertrophied. Mitral and aortic valves moderately thickened. Coronary arteries sclerotic. Aorta atheromatous. Two cusps were each 2 cm. wide, the two others together measured 2 cm. No corpus Arantii on smaller which was 8 mm. wide by 6 mm. deep, and fenestrated near free margin. Larger of two 14 mm. wide by 10 mm. deep, had no corpus Arantii either. Two larger cusps had corpus Arantii.

64. a. Female, forty-four years old, clinical signs of mitral stenosis. Necropsy revealed mitral stenosis. Four equal sized cusps.

b. Female, fifty-four years old. Pulmonary tuberculosis. Four equal sized cusps.

c. Male, forty-eight years old. Tuberculosis of elbow. Four equal sized cusps.

d. Male, forty-six years old. Senile brain atrophy. One of cusps of small size.

65. a. Female, sixty-four years old. Extra leaflet between posterior and left leaflets, 1 cm. wide, other cusps of normal size.

b. Male, seventy-six years old. Cusps arranged as anterior, posterior, internal, and external. Of about equal size.

66. a. Cusps of equal size but little smaller than usual.

b. Two larger, one middle-sized, and one small cusp.

67. a. Male, sixty-five years old. Marked hypertrophy of both ventricles of heart. Pulmonary emphysema, arteriosclerosis, old cerebral apoplexy, cirrhosis of liver. Between anterior and left cusp, a rudimentary weak fourth cusp.

b. Female, thirty-seven years old. Hypertrophy of heart. Tuberculosis, cirrhosis of kidneys. Three cusps of equal size, fourth somewhat smaller, between anterior and right cusps.

c. Male, fifty-one years old. Four equal sized, delicate cusps. Three fenestrated.

68. Male, thirty-eight years. Ascending stairs caused palpitation of heart. Two years before death had "black fever" and from this time became drowsy and livid. Distended jugular veins. Rapid, feeble pulse. Weak heart impulse. First sound shorter and more flapping, second less distinct than normal. No murmurs. Anasarca. Erysipelas and gangrene of leg. Pericardial, pleural and peritoneal effusion. Heart enlarged. Right ventricle divided in two portions by an imperfect septum. Right auricle twice as thick as left. Columnae carnae of left ventricle small compared with right. Cusps of equal size. Each furnished with a corpus sesamoideum. Each cusp 0.9 inch in width. Circumference of pulmonary artery 1 inch greater than that of aorta. Dilated pulmonary conus.

69. Small supernumerary cusp between anterior and right cusp. Fenestrated.

70. Female, thirty-two years old, who died of carcinoma of breast. Marked dilatation of right ventricle. Left cusp replaced by two small separate cusps. Two larger cusps thickened along free margin.

71. Female, five months old. Child brought to hospital with sickness and diarrhea. No cyanosis. Loud diffused systolic murmur. Recent endocarditis tricuspid valve. Foramen ovale two-thirds closed. Right ventricle dilated and hypertrophied. Bicuspid aortic valve. Patent interventricular septum. Patent ductus Botalli. Cusps thickened and having many small granulations. Pulmonary artery expanded up to bifurcation.

72. Male, fifty-six years old. Enlargement of heart, mostly left side. Marked hypertrophy of right side. Mitral valve a little thickened. Chronic endoaortitis from arch to bifurcation, but no dilatation. Aneurysm of splenic artery. Dilatation of pulmonary conus and artery. Lowering of left posterior cusp caused incompetency of valve. Thickening of other cusps. A fourth cusp, small, recognized by a special small sinus of Valsalva.

73. Female adult. Died in sixth month of pregnancy following cardiopulmonary complications. Heart larger than normal. Right auricle much larger than left. Right ventricle dilated. Buttonhole mitral stenosis. Cusps well developed and closed well. Most internal cusp, near septum, largest in size, 22 mm. wide and 16 mm. deep. Proceeding to right, next cusp 19 by 12 mm. Third, 14 by 10 mm.; fourth, 17 by 13 mm. Last two fenestrated. Orifice of pulmonary artery at margin of insertion of cusps, 100 mm.

74. Female, forty-two years old. Articular rheumatism at age of twenty-seven years. Auricles and ventricles normal. Cusps of different sizes, all in excellent condition. Cusp most to left largest—34 mm. wide by 18 mm. high. Proceeding right on posterior wall of artery, second cusp 21 mm. by 15, third 18 by 7 mm., fourth 23 by 16 mm. Cusps fenestrated. Nodule of Morgagni in each perfectly developed.

75. a. Male, aged fifty-eight years, who died of pneumonia. Adherent pericardium. Large flabby heart. Fourth cusp very small, between anterior and left cusp, 8 mm. wide and 7 deep. Other cusps each 20 mm. wide and 15 mm. deep.

b. Female, aged sixty-four years, who died of uterine carcinoma. Four cusps situated like above mentioned case.

76. a. Male, eighteen years old. Chronic rheumatic endocarditis of mitral valve. Subacute bacterial endocarditis. Four cusps.

b. Female, aged forty-three years. Lobar pneumonia. Chronic pulmonary tuberculosis. Hypoplasia of left auricle and ventricle. Dilatation of right auricle and ventricle. Four cusps. Fibrous thickening at margin of pulmonary valve. Dilatation of pulmonary artery (10 cm. in circumference).

c. Male, fifty-four years old. Peritonitis following appendectomy. Slight hypertrophy of left ventricle. Small extra cusp between two anterior cusps.

d. Female, ten years old. Carcinoma of jaw. Slight hypertrophy left ventricle. Small additional cusp between left anterior and posterior cusps. Pulmonary stenosis. Thickening and fusion of all cusps of pulmonary valve.

77. Female, middle-aged. Heart hypertrophied, especially right side. Three cusps of normal size. Fourth like others in contour and formation, but smaller, being both narrower and less deep. Leaflets thinned at lunula and fenestrated.

78. Male, fifty-five years old. No physical signs of pulmonary valvular disease. Granular and fatty degeneration of kidneys. Anasarca. Heart weighed 25½ ounces. Both ventricles dilated, right greatly. Wall of left considerably, that of right slightly thickened. Aortic cusps thickened and calcified. Three cusps normal in appearance and equal. Fourth between posterior and right lateral segments, somewhat less than one-half width of others but of nearly same depth. Elongated slit-like fenestrations near edge. Sinus of fourth cusp communicated with that of posterior cusp.

79. One cusp much smaller than the others.

## CASE REFERENCES

1. Abbott, Maude E.: Unpublished Cases in the Medical Museum, McGill University, No. 13. 181,<sup>1</sup> No. 13. 181,<sup>2</sup> No. 13. 181,<sup>3</sup> personal communication.
2. Albrecht, R.: St. Petersburg. med. Wchnschr. 1: 1, 1876.
3. Aschoff, L.: Pathologische Anatomie; ein Lehrbuch für Studierende und Aerzte, Vol. 2, ed. 6, Jena, 1923, p. 11, G. Fischer.
4. Begbie, J. W.: (Beale's) Arch. Med. 2: 11, 1860-61.
5. Bernabei, C.: Riv. Clin. di Bologna, 3d s. 3: 59, 1883.
6. Bernard: Bull. Soc. Anat., Paris 55: 426, 1880.
7. Bizot: Mém. Soc. Méd. d'Observ., Paris 1: 371, 1837.
8. Boettcher, T.: Beiträge zur pathologischen Anatomie des Gefäß-Systems, Inaug. Diss., Dorpat, 1873.
9. Bonnamour and Bertoux: Lyon méd. 108: 223, 1907.
10. Brünighausen, A.: Virchows Arch. f. path. Anat. 82: 200, 1882.
11. Campbell, K.: J. Anat. & Physiol., London 30: 347, 1895.
12. Carter, C. H.: Tr. Path. Soc., London 24: 48, 1873.
13. Cassebohm: Quoted in Allero's Elementi di Fisiologia. Referred to by Penada.
14. Cattell, H. W.: Tr. Path. Soc., Philadelphia 15: 161, 1889-91.
15. Chevers, N.: Lond. M. Gaz. 38: 834, 1846.
16. Coleman, W.: Proc. New York Path. Soc. (1897-98) p. 134, 1899.
17. Crowder, T. R.: Tr. Chicago Path. Soc. 3: 156, 1899.
18. Dagnini, G.: Cuore e Circolaz 14: 363, 1930.
19. Decloux and Duvoir: Bull. Soc. Anat. de Paris 83: 441, 1908.
20. Delitzin, S. N.: Arch. f. Anat. u. Physiol., Anat. Abteil., p. 107, 1892.
21. De Vries, W. M.: Beitr. z. path. Anat. u. z. allg. Path. 64: 39, 1918.
22. Dilg, J.: Arch. f. path. Anat. u. Physiol. 91: 193, 1883.
23. Dubrueil, J. M.: Des anomalies artérielles considérées dans leurs rapports avec la pathologie et les opérations chirurgicales, Paris, 1847, J. B. Baillière et Fils.
24. Duckworth: Tr. Path. Soc., London, 17: 113, 1866.
25. Durand, M.: Lyon méd. 15: 498, 1874.
26. Francis: Lond. Med. Gaz. 38: 846, 1846.
27. Greenhow: Tr. Path. Soc., London 20: 98, 1869.
28. Grünwald, O.: Ueber einen Fall von vier Klappen im Aorten- und Pulmonalarterientostium sowie offenem Foramen ovale, Inaug. Diss., Bonn, 1915.
29. Guéneau de Mussy, H.: Bull. Soc. Anat. de Paris 2: 74, 1836.
30. Haldane: Edinburgh M. J. 5: Part 1: 560, 1859-60.
31. Hodenpyl, E.: Proc. New York Path. So. (1897-1898) p. 135, 1899.
32. Houck, G. H.: J. Tech. Methods 12: 167, 1929.
33. Huber, J. J.: Handschrift nro. 290. Quoted by Sömmering, S. T., Vom Baue des menschlichen Körpers, Frankfurt am Main, p. 28, 1792, Th. Gefäßlehre.
34. Jenner, W.: Tr. Path. Soc., London 3: 295, 1851.
35. Jenner, W.: Tr. Path. Soc., London 4: 102, 1852-53.
36. Jianu, I., and Tovar, S.: Rev. Stiint. med. 17: 97, 1928.
37. Keith, A.: Lancet 2: 435, 1902.
38. Klob, J.: Med. Jahrb., Wien 2: 101, 1861.
39. Kolisko, E.: Ztschr. d. k.-k. Gesellsch. d. Aerzte zu Wien 15: 113 and 257, 1859.
40. Laignel-Lavastine: Bull. Soc. Anat. de Paris 75: 57, 1900.
41. Lamb, D. F.: in Löschner and Lamb: Aus dem Franz Josef-Kinder-Spitale in Prag, p. 101, 1860.
42. Landouzy: Bull. Soc. Anat., Paris 13: 305, 1838.
43. Launois, P. E., and Villaret, M.: Bull. Soc. Anat., Paris 80: 573, 1905.
44. Lindenberg, O.: Zwei Fälle von Herzen mit vier Semilunarklappen der Arteria pulmonalis, Würzburg, Inaug. Diss., 1893.
45. Martinotti, G.: Gazz. d. clin., Torino 23: 273, 1886.
46. Martinotti, G., and Sperino, G.: Arch. ital. de biol., Turin 6: 181, 1884. (Translated from Atti. d. r. Accad. di med. di Torino 6: 187, 1884.)
47. Meckel, J. F., Jr.: De cordis Conditionibus abnormibus, Halle, p. 31, 1802.
48. Meckel, J. F., Jr.: Tabulae anatomico-pathologicae, Fasc. 1, Tab. 2, Fol. Lipsae, 1817-26.
49. Mollier, G.: Anat. Anz. 78: 257, 1934.
50. Mönckeberg, J. G.: in Henke-Lubarsch Handbuch der speziellen path. Anat. u. Histol. 2: p. 153, 1924.
51. Morgagni, G. B.: De Sed. et Causes Morb., vol. 3, letter 34, article 15, 1761.
52. Osler, W.: Montreal Gen. Hosp. Rep. 1: 284, 1880.
53. Osler, W.: Tr. Path. Soc., Philadelphia 13: 302, 1886.

54. Peacock, T. B.: Tr. Path. Soc., London 3: 295, 1851.
55. Peacock, T. B.: Tr. Path. Soc., London 14: 126, 1863.
56. Penada, J.: Saggio terzo d'osservazioni e memorie patologico-anatomiche del dott. Jacopo Penada, Padova, p. 43, 1804.
57. Petsche, J. Z., Sylloge Anaticarum Selectarum Observationum Continentur, Halle, § 47, p. 14, 1736.
58. Pott, R., Jahr. f. Kinderh. 13: 11, 1879.
59. Read, W. T., and Krumbhaar, E. B.: M. Clin. North America 16: 238, 1932.
60. Riesman, D.: Proc. Path. Soc., Philadelphia o. s. 20 (n. s. 2): 264, 1898-99.
61. Sangalli, G.: Memorie del R. Istit., Lombardo, d. sc. e. lett. Milano, 3d s. 6: 297, 1885.
62. Schwalbe: Virchows Arch. f. path. Anat. 119: 28, 1890.
63. Simonds, J. P.: Am. J. M. Sc. 166: 584, 1923.
64. Simpson, F. O.: J. Anat. & Physiol. 32 (n. s. 12): 679, 1898.
65. Swalm, C. J.: Proc. Phila. Path. Soc., n. s. 16-17: 49, 1914-15.
66. Taruffi: Sulle malattie congenite e sulle anomalie del cuore, Bologna, Gamberini and Parmeggiani, p. 79, 1875.
67. Thilo, L.: Zur Kenntniss der Missbildungen des Herzens, Inaug. Diss., Leipzig, 1909.
68. Thompson, T.: Med. Chir. Tr., London 25: 247, 1842.
69. Thorel: in Lubarsch-Ostertag Ergebnisse der allgemeinen Pathologie, Morphologie u. Physiologie, v. 9, I abt., p. 604, 1903.
70. Thorel: München. med. Wehnschr. 53: 1688, 1906.
71. Tirard, N.: Tr. Path. Soc., London 32: 41, 1881.
72. Virchow, R.: Berl. Klin. Wehnschr. 35: 679, 1896.
73. Viti: Boll. d. soc. tra i cult. d. sc. mediche in Siena 3: 113, 1885.
74. Viti: Sperimentale 58: 329 and 441, 1886.
75. Wallman, H.: Oesterr. Ztschr. f. prakt. Heilk. 6: 429, 1860.
76. Wauchope, G. M.: Quart. J. Med. 21: 383, 1928.
77. Wilson, J. C.: Tr. Path. Soc., Philadelphia 6: 79, (1875-6) 1877.
78. Wilson, J. C.: Tr. Path. Soc., Philadelphia 7: 57, (1876-7) 1878.
79. Zoja: Il Gabinetto di Anatomia Umano Dell' Università di Pavia, Serie E, p. 187, nro. 47, 1874-87.

#### GENERAL REFERENCES

80. Gibson, G. A.: Jugular Reflux and Tricuspid Regurgitation, Edinburgh M. J. 25: 979, 1879-80.
81. Hill, L., Flack, M., and Holtzman, W.: The Measurement of the Systolic Blood Pressure in Man, Heart 1: 73, 1909-10.
82. Longworth, L. R.: Why Are the Segments of the Semilunar Valves Three in Number? Clinic, Cincinnati 14: 73, 1878.
83. Pezzi, C., and Silingardi, S., À propos d'un Cas d'ectasie de l'artère pulmonaire avec insuffisance de l'appareil valvulaire; signe radioscopique d'insuffisance pulmonaire, Bull. et mém. Soc. méd. d. hôp. de Paris 49: 117, 1925.
84. Pitt, G. N.: Right-Sided Valvular Diseases, in Allbutt and Rolleston's System of Medicine, London, 1909, vol. 6: p. 310.
85. Sansom, A. E.: The Diagnosis of Diseases of the Heart and Thoracic Aorta, London, 1892, Chas. Griffin & Co., p. 297.
86. Schwartz, S. P.: The Radiographic Evidence of Pulmonic Insufficiency, AM. HEART J. 2: 407, 1927.

## Department of Clinical Reports

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### THE IMPORTANCE OF RIGHT AXIS DEVIATION IN THE DIAGNOSIS OF PULMONARY STENOSIS\*

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THE greatest degree of right axis deviation in the electrocardiogram is seen in cases of congenital pulmonary stenosis. This fact has been recognized since the pioneer work of Einthoven. A corollary of this, that in the absence of right axis deviation a diagnosis of congenital pulmonary stenosis should be questioned, was confirmed by the autopsy findings of a case seen in consultation at the San Diego County General Hospital.

#### CASE REPORT

The patient, a boy twelve years old, had always been well except for scarlet fever at eight and diphtheria at nine years of age. When he was eight years old, before the attacks of scarlet fever and diphtheria, his parents had been told that he had "heart trouble," but no further information as to the nature of the cardiac lesion could be obtained. He had not had rheumatic fever. There had been no symptoms of cyanosis or of dyspnea.

The onset of the present illness, nineteen days before admission to the hospital, had been sudden and was characterized by general malaise, headache, nausea, vomiting, and fever. These symptoms had persisted and for the last week he had suffered also from dyspnea and palpitation of increasing severity.

Upon admission to the hospital the patient presented the picture of an acute fulminating bacterial endocarditis. The temperature was 104.6° F.; the pulse rate, 140; and the respiratory rate, 64. Cutaneous and conjunctival petechiae were present. Resonance was diminished over the bases of both lungs, and many coarse râles were heard over both lower lobes; roentgen ray examination revealed multiple areas of mottled infiltration throughout both lungs and passive congestion of the lower lobes. The left border of cardiac dullness extended 9 cm. from the midline. A palpable systolic thrill was present over the second interspace just to the left of the sternum, and a loud systolic murmur was heard over the entire precordium, of maximum intensity over the same area. The pulmonic second sound was present, however, and even somewhat accentuated. A teleroentgenogram showed the right border of the heart extending 5 cm. from the midline, and the left border, 8.8 cm. The internal diameter of the chest was 24 cm. The electrocardiogram showed a regular sinus rhythm with a rate of 140; the P-R interval, 0.15 sec.; the QRS interval, 0.05 sec.; and no abnormal axis deviation or other abnormalities (Fig. 1). The abdomen was slightly distended. There was no enlargement of the liver or spleen. The blood count revealed a moderate grade of anemia and marked leucocytosis (erythrocytes 3,790,000; hemoglobin, 68 per cent [Newcomer]; leucocytes, 27,000, of which 89 per cent were neutrophils and 11 per cent lymphocytes). Blood culture yielded a growth of staphylococci.

\*From the Rees-Stealy Clinic.

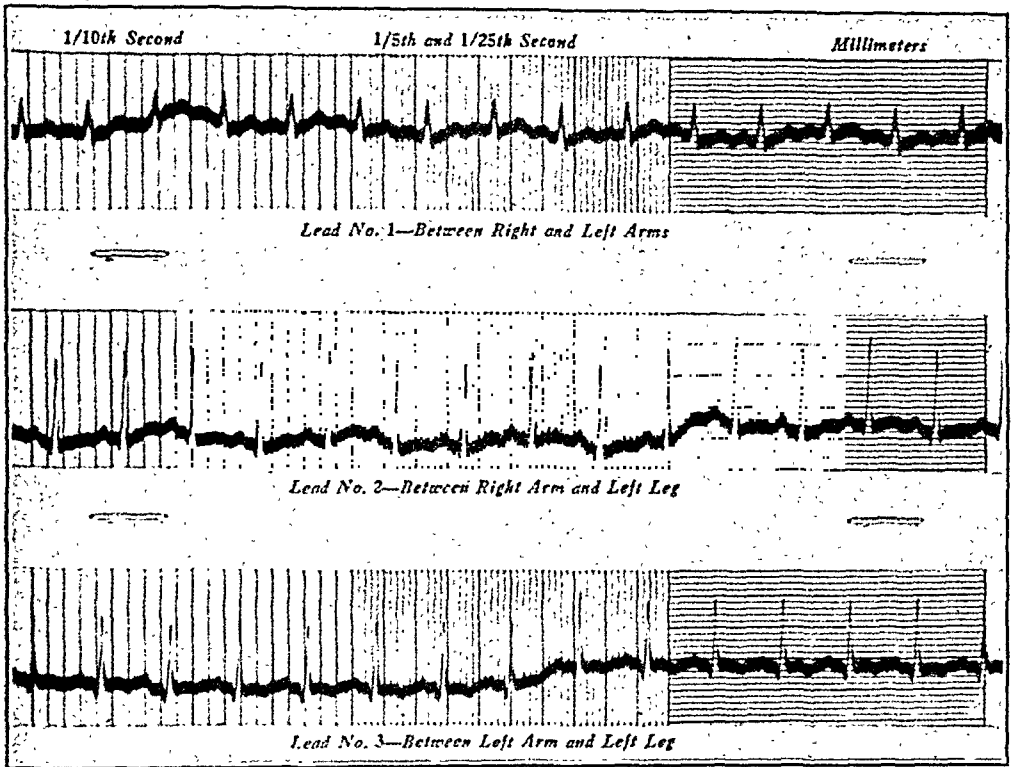


Fig. 1.—Electrocardiogram taken two days before death showing normal electrical axis. There is flattening in Lead II and inversion in Lead III of the T-waves but no significant abnormality except sinus tachycardia.



Fig. 2.

Fig. 3.

Fig. 2.—The chamber of the right ventricle showing the cauliflower-like mass of vegetations arising from the margins of a defect in the membranous interventricular septum and extending into and almost filling the pulmonary infundibulum and pulmonary valve orifice. The pulmonary valve is normal.

Fig. 3.—The chamber of the left ventricle showing a congenital defect (A) in the membranous interventricular septum. The abnormal opening is almost filled with vegetations of acute bacterial endocarditis. The aortic valve is normal.

The patient's condition grew progressively worse, and he died on the fourth day after admission to the hospital.

The essential findings at autopsy were the petechiae of the skin and beneath the capsules of the kidneys, multiple small septic infarcts of both lungs, and the cardiac findings. The heart weighed 210 gm. There was moderate hypertrophy of the left ventricle and slight hypertrophy of the right. A cauliflower-like mass of vegetations was found almost to occlude the pulmonary valve orifice, but with no attachment to the valve or to the pulmonary infundibulum (Figs. 2 and 3). The vegetations arose from the margins of a defect in the membranous interventricular septum, practically filled the opening, and extended into the left ventricle for about 2 mm. All of the valves were normal, and there was no other endocardial involvement.

#### DISCUSSION

A clinical diagnosis of congenital pulmonary stenosis complicated by acute bacterial endocarditis had been made in this case. The presence of an abnormal communication between the right and left sides of the heart was suspected because of embolic phenomena of both the systemic and pulmonary circulations, but the chief reason for doubting the correctness of this diagnosis was the normal electrical axis of the electrocardiogram. It was felt that a diagnosis of congenital pulmonary stenosis was incompatible with the absence of right axis deviation in the electrocardiogram. This opinion was confirmed at autopsy when the cause of the systolic murmur and thrill over the pulmonic area present during life was found to be not stenosis but almost complete occlusion of the pulmonary valve orifice by a mass of vegetations. These vegetations arose from bacterial endocarditis of a congenital interventricular septal defect. The predilection for a congenital lesion as a site of invasion by bacterial infection, rather than normal valves or endocardium, is shown by the findings in this case. The pulmonary valve was not involved by the infection in spite of its proximity. A condition of functional stenosis of the pulmonary valve which must have caused an appreciable degree of right ventricular strain was present during the terminal illness. However, insufficient time had elapsed between the onset of the bacterial invasion and the fatal termination of the disease (twenty-three days) to result in any remarkable hypertrophy of the right ventricle. This explains the normal electrical axis shown in the electrocardiogram.

#### SUMMARY

A case of acute bacterial endocarditis complicating a congenital defect in the interventricular septum is reported. The physical findings of pulmonary stenosis were explained at autopsy by a mass of vegetations which almost completely filled the pulmonary valve orifice but which arose from the margins of the interventricular septal defect. The inaccuracy of a diagnosis of congenital pulmonary stenosis in the absence of right axis deviation in the electrocardiogram is illustrated by this case.

## TRAUMATIC RUPTURE OF A NORMAL AORTIC VALVE\*

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A REVIEW of the literature to the year 1928 by Howard<sup>1</sup> revealed 113 cases of ruptured aortic valve as the result of muscular effort or trauma; the first case was reported in 1830 by Plenderleath.<sup>2</sup> Of this entire group only forty-seven cases were due to trauma and of these there were only fourteen<sup>3-16</sup> that were proved by autopsy. A search of the literature up to the present time failed to reveal any additional cases of the proved traumatic group, therefore the one here reported makes a total of fifteen cases and is the third reported in America.

### CASE REPORT

K. S., a single white male, aged twenty-two years, with a negative family and past history was injured in an explosion during the construction of the Ohio State Office Building on April 14, 1932. He was completely buried by stone and débris which caused the following external injuries: a comminuted fracture of the left forearm, compound fracture of the left leg, fracture into the left antrum, laceration of the left hip, laceration of the right hand, contusion of the left eye and side of face, fracture of the sternum, and discoloration of the entire anterior and posterior thorax due to contusions.

In an unconscious state he was admitted to the hospital where he received the necessary surgical attention, and on regaining consciousness he first complained of pain at the site of the compound fracture of the left leg, but within a few minutes he described a crushing sensation in his left chest associated with severe dyspnea. Five weeks following the injury he had an elevation of temperature for seven days, which was due to slight infection in his left leg. The recovery from his external injuries was good, and in December, 1932, he was discharged from the hospital, but all during this time he continued to have the crushing sensation in the left chest, moderate dyspnea which became severe on exertion, moderate palpitation on exertion, frequent attacks of syncope, severe dizziness, and anxiety with a fear of impending death. During these attacks of severe dizziness and syncope he would first become pale and then develop cyanosis of the lips and fingernails. He had a low grade infection in the left antrum which had been fractured, but it responded very well to treatment. In June, 1933, he was again admitted to the hospital because of signs of heart failure, and a pain in the right kidney region. Two days later, on June 16, 1933, death due to heart failure occurred.

This patient was known personally for ten years prior to his injury and had frequently been examined, the last time on Dec. 2, 1930, when he was found normal in every respect, with a normal, regular heart and a blood pressure of 120 mm. systolic and 76 mm. diastolic.

Cardiologic examination two days before death revealed engorgement of the neck veins, marked swinging of the carotid arteries, and a marked pulsation in the supra-sternal notch. The apex beat was not palpable, and the cardiac dullness in the fifth interspace was 10 cm. to the left of the midsternal line, and in the fourth

\*From the Cardiologic Departments of White Cross and Children's Hospitals and the Medical College of Ohio State University, Columbus, Ohio.



interspace 5 cm. to the right of the midsternal line. There was a loud rough diastolic murmur heard at the base of the heart and along the left border of the sternum, with the maximum intensity at the aortic area. There was also slight roughness of the first sound at the apex. The rhythm of the heart was regular, and the rate was 96. The pulse was of the Corrigan type, and the blood pressure was systolic 110 mm., diastolic 20 mm. The liver edge was at the costal margin and not tender. There were many moist râles in the bases of both lungs. The urine contained a large amount of albumin, no sugar, but many red blood cells and pus cells, and the blood count showed 80 per cent hemoglobin, R.B.C., 4,320,000, W.B.C., 15,200. Orthodiagram showed the transverse diameter of the heart to be 15.5 cm. The Wassermann reaction was negative. The diagnosis was traumatic heart disease, ruptured aortic valve, aortic insufficiency, myocardial insufficiency, and heart failure—with, as an associated condition, possible embolism into the right kidney.



Fig. 1.—Ruptured and fragmented cusps of the aortic valve.

*Autopsy.*—The body was that of a well-developed and fairly well-nourished white man, measuring 67½ inches in length and estimated to weigh about 160 pounds.

After dissection of the superficial tissues from the anterior chest wall and incision through the costochondral junctions of the ribs, the sternum was elevated. In elevating the sternum preparatory to its removal for the examination of the thoracic viscera, it was found to be separated at the synchondrosis sternalis between the manubrium and the body of the sternum in such a manner that it could be easily hinged outward, because there was no osseous union as is usually found in a man of this age. The periosteal fibers supporting this synchondrosis were relaxed so that the body of the sternum could be easily displaced backward into the mediastinum to the extent that it would override the lower margin of the manubrium sterni. No fractures of the ribs or clavicles were demonstrated.

The cardiac area was normal in size and the pericardial sac contained the usual amount of clear fluid. The visceral and parietal pericardium was smooth and

glistening. When the heart was removed and opened, the myocardium of the left ventricle was of the usual thickness and of good consistency. The mitral valve was normal. The various cusps of the aortic valve were partially covered with precipitated blood and were ragged (Fig. 1). A careful examination of the various cusps of this valve revealed a transverse slit just below the margin of the left posterior cusp. The right posterior cusp was irregularly torn, fragmented and infiltrated with blood, and the anterior cusp was also extensively torn. There was no gross evidence of inflammatory reaction, the process present was that of an unhealed rupture and fragmentation of the valve cusps. The valve was entirely incompetent. At the base of the anterior cusp the adjacent myocardium and subpericardial adipose tissue was discolored a dark reddish brown which discoloration was apparently due to an old hemorrhagic infiltration. The coronary orifices were patent, and a dissection of the coronary arteries showed no pathological changes. The aorta was smooth and normal throughout the entire length. The myocardium of the right ventricle and also the pulmonary and tricuspid valves were normal.

Both lungs were free from adhesions, and there was a small amount of pleural fluid. Removal and cut section revealed the left lung to contain a moderate amount of edematous fluid and diffuse congestion. This process was most marked in the lower lobe. The right lung was similar throughout but the process of congestion was less marked than in the left lung. There was no evidence of pneumonic consolidation, embolism or infarction. The mediastinum was normal, and there was no enlargement of the lymph glands.

The various viscera of the abdominal cavity were normal except the right kidney which showed a large area of infarction.

*Microscopic Sections.*—The microscopic sections that were taken through the ruptured cusps of the aortic valve showed a quite thin central fibrous structure and on both surfaces of the valve a precipitate of hemorrhagic material. Immediately adjacent to the fibrous tissue of the valve was a thin layer of plasma cells and a small amount of fibrin, while external to this red blood cells were arranged in a granular material simulating the precipitation type of blood clot. There was no evidence of inflammation or of repair, and the only reaction was the layer of plasma cells.

The sections taken through the myocardium and subpericardial tissue at the base of the aortic valve showed infiltration with round cells and mononuclear cells, and throughout the entire section there was an extensive deposition of blood pigment.

The sections taken through the other portions of the myocardium were normal.

The sections taken through both lungs revealed the alveolar spaces filled with edematous fluid, in which there were a few blood cells. There was a moderate desquamation of the alveolar epithelium in the sections from the lower lobe of the left lung. Many of the alveoli contained heart failure cells.

The sections of the spleen and liver were normal.

The sections of the right kidney that were taken through the area of infarction showed a complete destruction of the kidney tissue in this area and replacement with a hyalinized homogenous material.

*Diagnosis:* Rupture of the aortic valve, hemorrhagic infiltration about the base of the aortic valve, separation and dislocation of the sternal synchondrosis, bilateral congestion and edema of the lungs, multiple scars over the extremities, and deformity of the left arm and left leg.

## DISCUSSION

Traumatic rupture of the aortic valve cusps has occurred most frequently after muscular effort or strain, but a few cases of which fourteen have been proved by autopsy, have occurred following injury

such as falling from a height or a blow to the chest. Barié and Potain<sup>9</sup> produced rupture of the aortic valve by striking with a hammer a board fixed over the precordium of a cadaver. Dufour<sup>17</sup> and Kuelbs<sup>18</sup> were both able to produce rupture of the aortic valve by blows struck to the left chest of the dog. In the case presented, the rupture to the cusps of the aortic valve was caused by the crushing injuries to the thorax incidental to burial under stone and débris. It is unusual that all the cusps of the valve were ruptured and that, while two cusps were fragmented, one contained a transverse perforation. Rupture to the aortic valve occurs most frequently in diseased valves, but in this case a normal valve was injured. The immediate pain in the left chest associated with dyspnea is the most frequent and characteristic symptom of traumatic heart disease. The attacks of syncope and the classical signs of aortic insufficiency aid in the diagnosis of traumatic rupture of the aortic valve during life, especially if the heart has been examined and known to be normal before the accident. These facts should be kept in mind because it is evident that traumatic heart disease is frequently overlooked and that a surprising number of physicians are of the opinion that injury to the normal heart is almost impossible.

#### SUMMARY

A case of rupture of the cusps of a normal aortic valve is reported. The most frequent and characteristic symptom of traumatic heart disease seems to be pain in the left chest associated with dyspnea. The possibility of diagnosis of traumatic rupture of the aortic valve during life depends greatly upon whether the heart had been examined and found normal before the accident.

#### REFERENCES

- Howard, C. P.: Aortic Insufficiency Due to Rupture by Strain of a Normal Aortic Valve, *Canad. M. A. J.* 19: 12, 1928.
- Plenderleath, London *M. Gaz.* 7: 109, 1830.
- Bouillaud (Bergeon): *Traité Clinic des Maladies du coeur*, Paris 2: 626, 1841, J. B. Baillière.
- Wilks, S.: *Tr. Path. Soc. Lond.* 16: 77, 1865.
- Hayden, T.: *Dublin Quart. J. Med. Sc.* 44: 438, 1867.
- Finnell: *New York M. Record* 2: 283, 1867.
- Foster, B.: *Brit. M. J.* 2: 718, 1873.
- Duroziez, P.: *L'Union Med.* 29: 922, 1880.
- Barié, E. (Potain): *Rev. de méd.* 1: 132, 309, 482, 1881.
- Mader, J.: *Ber. d. k. k. Krankenanst. Rudolph-Stiftung in Wien*, p. 391, 1886.
- Biggs, H. M.: *New York M. J.* 2: 76, 1890.
- Strassman, F.: *Ztschr. f. klin. Med.* 42: 347, 1901.
- Schmidt, M. B.: *München. med. Wehnschr.* 49: 1565, 1902.
- Tranquilli, E., and Deganello, U.: *Riforma med.* 24: 337, 1908.
- Steinitz, E.: *Deutsches Arch. f. klin. Med.* 99: 139, 1910.
- Meyer, E. C.: *Med. klin.* 16: 525, 1920.
- Dufour, C.: *Thèse de Paris*, 1896, p. 76.
- Kuelbs: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 19: 678, 1909.

# SYMMETRICAL GANGRENE OF THE EXTREMITIES ASSOCIATED WITH PURPURA

REPORT OF A CASE IN WHICH ERGOTISM WAS SUSPECTED\*

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SINCE Raynaud's classic report, "Local Asphyxia and Symmetrical Gangrene of the Extremities," in 1862, reports of cases of symmetrical gangrene frequently have appeared under the misnomer of "Raynaud's disease." The unusual features found in a case of symmetrical gangrene, which was seen at the clinic in the past year, would seem to merit a report of this case.

## REPORT OF CASE

A man, aged forty-four years, a Norwegian farmer who lived in Montana, came to the clinic on June 17, 1935, complaining of loss of eyesight, and gangrene of the hands and legs. For two weeks prior to the onset of the acute phase of his present illness, he had not been feeling well, although he had not had any specific symptoms. On March 30, 1935, he had a mild sore throat. The next day he became acutely ill with chilly sensations, nausea, vomiting, diarrhea with tarry stools, and severe burning pain, which involved the entire body but was most severe in the extremities. The left hand was blue and cold. These symptoms persisted until the next day when he was seen by his family physician.† At that time his temperature was 102.2° F., the pulse rate, 124; and the respiratory rate, 38. Scattered over his entire body, but particularly over the extremities, were many purpuric and ecchymotic spots. A few spots also were observed throughout the mucous membrane of the nose, mouth, pharynx, and the conjunctivae. The gums were spongy and bled very easily. The lips, tongue, and soft palate were badly swollen, and the latter bled from the slightest trauma. Swelling and tenderness of the elbows, knees, and ankles were noted, but there was no redness. Passive movement of these joints produced pain, which was completely relieved by rest. The spleen was tender and large enough to be palpated. The burning pain disappeared within forty-eight hours, but paresthesia persisted for several weeks. Examination of the urine revealed considerable amounts of blood and albumin. The number of erythrocytes and leucocytes was normal, and the platelets numbered 150,000 per cubic millimeter of blood. The stools were tarry in appearance, and examination revealed the presence of blood.

For the next few days after the onset, the patient was severely ill. On the second day of his illness, many of the purpuric spots on the extremities began to appear gangrenous. On the fourth day he suddenly became almost blind and was able to distinguish only the outline of objects. He then became somnolent, irrational, and his condition was considered grave. However, within a period of three or four days he had begun to improve. He became rational again, his temperature subsided; the painful joints improved remarkably, and at the end of two weeks the acute phase of his illness appeared to be over. All of the purpuric spots on the head, trunk, and mucous membranes disappeared without leaving any trace of their presence.

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†We are indebted to Dr. T. M. Morrow of Scobey, Montana, for a detailed account of the onset of the patient's illness.

The sequelae involved the eyes and extremities. The visual impairment, along with photophobia and some redness of the conjunctivae, persisted until the patient came to the clinic on June 17. The gangrenous spots became more marked than they had been, and gradually involved the distal two-thirds of the thumb and the index, middle, and ring fingers on the right hand; the tips of the middle and little fingers on the left hand, a small portion of the dorsal surface of the middle finger on the left hand; almost the entire outer surface of the left leg; a small portion of the outer aspect of the right leg; all of the toes of the right foot, and a part of the distal and lateral portions of the plantar surface of the right foot.

Following the acute phase of his illness, he noted numbness in his hands and feet, and loss of sensation in his legs and feet. About eight weeks after the onset of the condition, all the toes of the right foot sloughed, and a short time thereafter the gangrenous spots on the outer aspect of the left leg sloughed and left a large ulcer. Gradually, all of the gangrenous spots on the lower extremities sloughed, and partial healing occurred. However, the gangrenous spots on the fingers remained.

An interesting side light on the patient's illness was the coincidental illness and death of his mother. The patient and his mother had lived together for many years. Apparently, the mother, who was sixty-four years of age, had been suffering for some time with a mild congestive heart failure. Two days after the onset of her son's illness, she suddenly became acutely ill; she vomited, had diarrhea, and passed tarry stools. When seen within twenty-four hours by her family physician, she was acutely ill and stuporous. She had a marked congestive heart failure, dyspnea, cyanosis, and edema which extended up over the lower part of the abdomen. On her forehead and thorax there were petechial spots, and a few hours before her death similar spots were noted on her abdomen and lower extremities. These spots were similar to those which were noted on the son, but were less extensive. She died suddenly within twenty-four hours of the onset of her illness. Necropsy was not permitted.

When examined at the clinic, the son was well developed but poorly nourished. The value for the systolic blood pressure was 98 mm. of mercury, and that for the diastolic was 60 mm. of mercury. The pulse rate and the temperature were normal.

There was marked impairment of vision. With the right eye he could distinguish moving objects, but in the left eye only light perception remained. A bilateral sub-acute uveitis was present. Bilateral cataracts were present, and both pupils were completely adherent.

Examination of the upper extremities revealed that the ulnar and radial arteries were pulsating normally. On the right hand the distal two-thirds of the thumb, index, middle, and ring fingers, and the tip of the little finger were dry, black, and completely gangrenous (Fig. 1). On the left hand, a similar condition involved the distal third of the middle finger, the tip of the little finger, and a small spot on the dorsum of the middle finger in its middle third. The line of demarcation between the healthy and gangrenous portions was clean-cut, and healthy granulations were noted proximally at the line of demarcation. The hands and the fingers were warm up to the line of demarcation and did not reveal any evidence of arterial insufficiency.

Examination of the lower extremities revealed that the popliteal, dorsalis pedis and posterior tibial arteries were pulsating normally. Each of the toes of the right foot had sloughed either at the distal or proximal interphalangeal joints, and the stumps were almost healed (Fig. 2). There were ulcers on the plantar surface of the right foot and on the lateral aspect of the lower third of the right leg with evidence of recent healing of several small ulcers in this situation. On the left leg there was a very large ulcer which involved almost the entire lateral aspect of this leg. There was evidence of recent healing in its upper margins. The toes of the

left foot were not involved. There was fairly healthy appearing granulation tissue at the bases of the ulcers, and there was evidence of recent healing around their margins. The ulcers were very insensitive to pain, as were the entire legs and feet. The feet presented no clinical evidence of arterial insufficiency.

Neurological examination revealed mild to moderate loss of touch and pain sensation in the legs and feet. The sensory changes in the legs and feet were noted to be most marked peripheral to the ulcers. The neurological diagnosis was mononeuritis multiplex, which probably was the result of infarctions.

Laboratory examination revealed the concentration of hemoglobin to be 12.6 gm. in each 100 c.c. of blood; the erythrocytes numbered 4,170,000; the leukocytes, 5,800; and the platelets, 158,000, respectively, per cubic millimeter of blood. Urinalysis on two occasions did not reveal any abnormality. The blood flocculation test was negative. Examination of the urine did not disclose lead or arsenic. A roentgenogram of the thorax was normal. Nasal smears did not reveal *Mycobacterium leprae*. Examination of the spinal fluid revealed normal findings. Agglu-

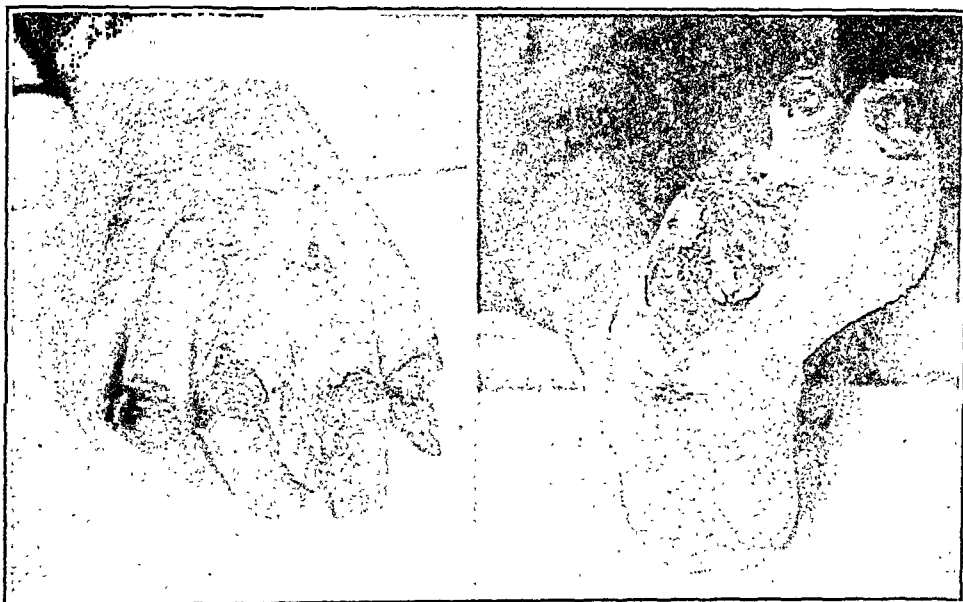


Fig. 1.

Fig. 2.

Fig. 1.—Gangrene of fingers.

Fig. 2.—Healing of stumps and large ulcerated region in gangrene of foot.

mination tests for typhoid and paratyphoid fever and with *Proteus* X 19 were negative. Nygaard coagulation studies gave a normal coagulation index and platelet volume.

On June 24, 1935, pinch grafts were applied to the ulcerated region on the left leg. The first, second, third, and fourth fingers of the right hand and the first and fifth fingers of the left hand were amputated at the line of demarcation. The grafts took satisfactorily, and the wounds were healing rapidly when the patient was dismissed on September 7, 1935.

The patient returned to the clinic on October 20, 1935. Examination at this time disclosed that the fingers and the ulcers on the left and right legs had healed. Two small ulcers on the plantar surface of the right foot were still open. Examination of the eyes revealed that the uveitis had subsided considerably; otherwise, the eyes were essentially the same as they were when the patient was seen previously. Urinalysis did not reveal any abnormality. There were 339,000 platelets per cubic millimeter of blood. On October 30, a combined extraction of an immature cataract was performed on the right eye. The patient was dismissed December 21, 1935. His chief concern now is his vision.

## COMMENT

The diagnostic problem presented by this patient is an interesting though very difficult one. No similar condition had been observed in more than 3,500 cases of peripheral vascular disease seen at the clinic in the previous ten years. The differential diagnosis would seem to demand consideration of a toxic, infectious, or allergic condition.

Careful inquiry did not reveal any possible causative agent, with the exception of a home-ground, whole wheat cereal which the patient and his mother had been eating for several months. Ergot poisoning, therefore, was considered as a possible etiological agent. Ergot is an important disease of rye, wheat, barley, and wild grasses in many sections of the United States. Although gangrenous ergotism has been reported among cattle in Iowa,<sup>10</sup> no case in which ergotism of human beings was the result of the ingestion of ergotized grain or grain products has been reported in this country.

There are certain features in this case which fit the description of ergotism, as given by Barger. In the various epidemics two types of the disease have been noted, that is, the gangrenous and the convulsive. The epidemics have been predominately of one type or the other. The combined form in the same case is extremely rare. According to Barger, the symptoms which are common to both types are a feeling of intense heat and cold, burning pains (St. Anthony's fire) in the extremities, vomiting, severe diarrhea, formation of red and violet spots and vesicles in the skin, and impairment of mental function. In the gangrenous form, the skin becomes cold and livid and the diseased part may become black and gangrenous very suddenly. In the convulsive form, severe mental reactions, paresthesias, muscular spasms, and convulsions occur, and in some cases there is a residual anesthesia of the skin and even permanent contractures of the muscles and paralysis of the extremities. Visual disturbances are common in convulsive ergotism, and cataracts have been reported in many of these cases.<sup>3</sup> The disease may come on acutely and progress rapidly in either type. There is no mention of the state of the temperature or of the occurrence of gastrointestinal hemorrhages in any of the previous accounts of the disease.

The facts that both the patient and his mother had been eating whole wheat cereal for a considerable time and that both were similarly afflicted at about the same time are suggestive of poisoning with ergot. The occurrence of the burning pain over the entire body and its disappearance the following day, with subsequent development of partial anesthesia of the limbs, are significant. The paresthesias and severe mental reaction and subsequent development of cataracts would indicate that this was a mixed form of the disease. Purpura and thrombocytopenia have been reported to occur following the ingestion of ergot.<sup>6</sup> The violet and red vesicles and spots in the skin, which were observed in previous epidemics, may have been of a purpuric nature.

An analysis of a sample of the whole wheat cereal obtained from the same mill, though of a different batch from that eaten by the patient and his mother, revealed no trace of ergot, as analyzed by Schaer's method. This negative finding is of doubtful significance since an examination was not made of the cereal which the patient was eating at the onset of his illness.

The occurrence of symmetrical gangrene in acute infectious processes has recently been pointed out by Lewis.<sup>5</sup> Typhus fever, typhoid fever, pneumonia, influenza, diphtheria, scarlet fever, and measles are examples of infectious diseases which have been complicated by symmetrical gangrene. The acute phase of this patient's illness might well have been the result of an infectious process of some kind. However, three months after the onset, agglutination tests for typhoid fever, paratyphoid fever, and typhus fever were negative.

Finally, the occurrence of purpura without a marked thrombocytopenia brings up for consideration the anaphylactoid type of purpura. The occurrence of gangrene as a complication of purpura is extremely rare. Both the purpura and the gangrene have almost always been secondary to some infectious disease, usually scarlet fever.<sup>4</sup> Meyer<sup>6</sup> recently reported a case of gangrene following purpura, in which there was a marked reduction in the number of blood platelets. Osler presented a series of cases of purpura in which the visceral manifestations were outstanding. In some of these cases there was necrosis of the skin. All of the patients had allergic manifestations such as angioneurotic edema, and many had had previous purpuric and allergic episodes. Our patient presented evidence of involvement of the eyes, gastrointestinal tract, spleen, and kidneys, which was not markedly dissimilar to that in the cases reported by Osler, and it is possible that the digital gangrene might represent another form of visceral involvement in the form of contraction of smooth muscle not unlike the contraction of the smooth muscle of the intestine, which characterizes Henoch's purpura. However, none of the subjects who had purpura and gangrene had severe burning pains which disappeared suddenly, paresthesias, marked impairment of mental function, or cataracts, such as are seen in ergotism.

#### SUMMARY

We have presented a case in which a farmer, aged forty-four years, had an acute illness of two weeks' duration, complicated by purpura and an extensive dry gangrene of the digits and of the skin of the legs. We feel that the etiological agent was toxic or infectious in origin, although it appears impossible at this late date to arrive at a definite diagnosis.

#### REFERENCES

1. Allen, E. V., and Brown, G. E.: Raynaud's Disease: A Critical Review of Minimal Requisites for Diagnosis, *Am. J. M. Sc.* 183: 187, 1932.
2. Barger, George: *Ergot and Ergotism*. London, 1931, Gurney and Jackson, 279 pp.



3. Bechterew, W. von: I. Ueber neuro-psychische Störungen bei chronischen Ergotismus, Neurol. Centralbl. 11: 769, 1892.
4. Dick, G. F., Miller, E. M., and Edmondson, Hugh: Severe Purpura With Gangrene of the Lower Extremity Following Scarlet Fever, Am. J. Dis. Child. 47: 374, 1934.
5. Lewis, Thomas, and Pickering, G. W.: Observations Upon Maladies in Which the Blood Supply to Digits Ceases Intermittently or Permanently and Upon Bilateral Gangrene of Digits: Observations Relevant to So-called "Raynaud's Disease." Clin. Sc. 1: 327, 1934.
6. Meyer, M. G.: Purpura Complicated by Cerebral Hemorrhage and Gangrene of the Lower Extremities, J. Iowa State M. Soc. 25: 491, 1935.
7. Osler, William: The Visceral Lesions of Purpura and Allied Conditions, Brit. M. J. 1: 517, 1914.
8. Peshkin, M. M., and Miller, J. A.: Quinine and Ergot Allergy and Thrombocytopenic Purpura: Report of a Case, J. A. M. A. 102: 1737, 1934.
9. Raynaud, A. G. M.: De l'asphyxie locale et de la gangrène symétrique des extrémités, Paris, 1862, Rignoux, 177 pp.
10. Weniger, Wanda: Ergot and Its Control, Bulletin No. 176, North Dakota Agriculture College, 1934.

# Society Transactions

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## NEW YORK HEART ASSOCIATION

### Heart Committee of the New York Tuberculosis and Health Association

The annual scientific meeting of the New York Committee on Cardiac Clinics was held at the New York Academy of Medicine in New York City on April 28, 1936. The following are abstracts of papers presented or read by title:

**The Precordial Lead in Children.** Arthur M. Master, M.D., Simon Dack, M.D., and Harry L. Jaffe, M.D. (Mount Sinai Hospital).

#### ABSTRACT

A preliminary report on chest leads in normal children has been made. Anterior chest leads were studied in seven positions in seventy-one normal children of from two to fifteen years of age. The active electrode was moved across the fourth or fifth interspace from the right of the sternum to beyond the apex of the heart. The following data were obtained: The P-wave was small, usually inverted and often absent. The Q-wave, always present, varied from 2 to 22 mm., increasing as the electrode approached the apex. The R-wave also varied from 2 to 22 mm., but diminished near the apex. Notching and slurring of the QRS were common. The R-T transition was never elevated or depressed over 1 mm. An upright or diphasic T-wave to the left of the sternum, abnormal in adults, occurred in 60 per cent of the children. It was most frequent over the sternum, the incidence decreasing as the apex was approached as well as with increasing age. No correlation was found between the shape of the heart or axis deviation and the presence of upright T-waves. An upright T-wave in the precordial lead in children is not to be considered a sign of cardiac involvement.

**Studies of the Circulation in Affections of the Precordium.** Harold J. Stewart, M.D., Norman F. Crane, M.D., and John E. Deitrick, M.D. (New York Hospital, Cornell University Medical College).

#### ABSTRACT

Studies of the circulation have been made in patients exhibiting lesions of the pericardium, three suffering from chronic constrictive pericarditis, and a fourth exhibiting recurrent pericardial effusion. Observations were made of cardiac output by the acetylene method (three samples being taken), of arm-to-tongue circulation time (decholin), of venous pressure (direct method), of blood pressure, of heart rate, of cardiac size (x-ray). *Electrocardiograms together with electrical axis shifts* were also recorded. All observations were made with patients in a basal metabolic state.

In those with constrictive pericarditis it was found that the cardiac output was less and the circulation time longer than in normal individuals; the venous pressure was elevated. The heart was not large in these patients, and the electrical axis of the electrocardiogram was relatively fixed.

In the patient with recurring effusion after removal of the fluid (1,000 c.c. to 1,500 c.c. was removed every three to four weeks), edema of the face, dyspnea, pleural

effusion, ascites, and swelling of the liver subsided or became less, only to increase or return with reaccumulation of pericardial effusion. In this patient in each instance recurrence of the pericardial effusion was associated with rise in venous pressure, decrease in cardiac output, lengthening of the circulation time, and increase in heart rate. At operation, the pericardial sac was thin and nowhere adherent, and no reason for the recurrence of the effusion was ascertained. Recovery after operation was uneventful, recurrence of the effusion continuing to take place.

*Summary.*—Affections of the pericardium which obstruct the filling of the heart were associated with increase in venous pressure, increase in arm-to-tongue circulation time, and decrease in cardiac output in the patients who have been studied.

#### **Heart Disease and Pregnancy.** Arthur E. Lamb, M.D. (Brooklyn Hospital).

##### ABSTRACT

Since 1926 a study of the relation of heart disease and pregnancy has been carried on in the prenatal division of the cardiac clinic. One hundred ten patients are the basis of this study.

Analyses were made covering the following points: (1) incidence of functional murmurs; (2) incidence of organic lesions; (3) etiology of the organic lesion; (4) anatomical diagnosis, and the relation of the anatomical diagnosis to heart failure and death; (5) the relation of the age of the patient to decompensation; (6) the relation of parity to heart failure; (7) the months of pregnancy in which heart failure occurs.

The number of decompensations and deaths occurring in each functional class is shown. It was found that twelve patients in Classes I and II A became decompensated. Analysis of the cases was made according to the size of the heart, the presence of a long rumbling diastolic murmur at the apex, the duration of the rheumatic disease, the presence of signs of rheumatic activity, and the presence of auricular fibrillation. From this analysis it was concluded that these factors in addition to the functional classification must be considered in the evaluation of a pregnancy risk.

#### **Coronary Artery Disease in Women.** Hyman Levy, M.D., and Ernst P. Boas, M.D. (Mount Sinai Hospital).

##### ABSTRACT

Although, in women, precordial pain is a very common symptom, coronary artery disease is unusual in the absence of diabetes and hypertension and is rare in women under fifty years of age. Ignorance of this fact leads to many mistaken diagnoses. During the past seven years in an office practice representing largely patients referred for cardiovascular diagnosis, we saw 171 cases of coronary artery disease in women, which represents 10.3 per cent of all of the women seen. In the same period we saw 1,059 cases of coronary artery disease in men, representing 49.6 per cent of all male patients. The frequency is 4.8 times as great in men as in women. Of the 171 cases in women, 73.7 per cent occurred in the presence of hypertension alone, 14 per cent in the presence of both diabetes and hypertension, and 3.5 per cent in the presence of diabetes alone. In only 8.8 per cent was there neither hypertension nor diabetes, and only one-third of this small group were women under fifty years of age. A large part of the study is devoted to the evaluation of symptoms and the establishment of criteria for the diagnosis of coronary artery disease in women. This is based largely on a follow-up study undertaken to check the accuracy of the original diagnosis.

**The Effect of Potential Variations of the Distant Electrode on the Precordial Electrocardiogram.** Charles E. Kossmann, M.D., and Bertha Rader, A.B. (New York University College of Medicine, Bellevue Hospital).

## ABSTRACT

Leads IV, V, and VI of Wolferth and his associates were recorded in nine subjects with widely varying electrical axes in the standard leads. The potential variations of the left leg, and of precisely the same points on the precordium and on the back used to record Lead IV, were then obtained by the method of Wilson and his associates. All electrocardiograms were taken simultaneously with standard Lead I. In every patient the potential variations of the precordial electrode qualitatively and quantitatively dominated the form of the curve obtained when this electrode was paired with a distant one placed either on the back or on the left leg. In Leads IV and V the effect of the distant electrode was usually small but exceedingly variable. When the position and size of the exploring electrode were kept constant, marked differences between Leads IV and V were due only to considerable differences between the potential variations of the back and the potential variations of the left leg.

*Papers Read by Title*

**Transient Ventricular Fibrillation: Its Clinical and Graphic Manifestations During Established Auriculoventricular Dissociation.** Sidney P. Schwartz, M.D. (Montefiore Hospital).

## ABSTRACT

Correlated observations of the clinical and graphic manifestations of syncopal seizures in six patients with A-V dissociation reveal that a clinical diagnosis of the cardiac mechanism responsible for these seizures may be made from a knowledge of the following:

A. The prefibrillatory mechanism. This is characterized by an acceleration of the basic ventricular rate. This acceleration may be effected through (a) a simple and progressive shortening of the interventricular periods; (b) a steplike progression of both auricles and ventricles; (c) the interposition of a single extrasystole changing a slower rhythm to a faster one; (d) recurrent short runs of tachycardia arising in an ectopic focus of the ventricles and alternating with the periods of heart-block; (e) a tachysystole in which a rapid auricular rate keeps pace with a rapid ventricular rate; and finally (f) the ventricular rate may be increased by isolated premature beats of the ventricles which would appear in rapid succession and accelerate the heart before the cardiac mechanism responsible for syncope set in.

B. The postfibrillatory mechanism which follows the revival of the heart. This is characterized by a progressive acceleration of an intermediary idioventricular rhythm, so that, if the heart rate following an attack of syncope is noted to increase in this manner, it is fair to assume that the period of syncope which anteceded this mechanism was the result of ventricular fibrillation.

C. The use of epinephrine hydrochloride. In patients in whom standstill of the ventricles is the cause of syncope, epinephrine hydrochloride merely accelerates the idioventricular rate or does not influence it at all. In patients in whom ventricular fibrillation is the underlying cardiac mechanism, epinephrine hydrochloride yields short runs of ventricular oscillations which are short runs of ventricular fibrillation.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### PROCEEDINGS OF THE GERMAN ASSOCIATION FOR THE STUDY OF THE CIRCULATION\*

EIGHTH ANNUAL MEETING, WIESBADEN, MARCH 24 AND 25, 1935

The main topic for this meeting was the interrelation of circulation and respiration. The following reports were made:

#### 1. The Physiological Coordination of Respiration and Circulation. W. R. Hess (Zurich).

A review of recent work was presented. The author first considered  $\text{CO}_2$  and  $\text{O}_2$  transport. Since the tissue cells are the source of  $\text{CO}_2$ , their blood flow must be adjusted to their  $\text{CO}_2$  production. This is done by means of the arterioles. The diversion of blood to active tissues leads to a decrease of blood supply to the respiratory center which decrease results in its stimulation, unless the cardiac output is augmented sufficiently to counteract the effect. Arterial reflexes resulting from the blood pressure changes further modify these adjustments. A balance exists between the  $\text{CO}_2$  transported to the lung by the blood and the  $\text{CO}_2$  eliminated by the lungs. This is regulated by the  $\text{CO}_2$  concentration of the blood acting reflexly on the respiratory center by stimulating certain receptors located in blood vessels. It follows, therefore, that every adjustment of the circulation which alters the concentration of  $\text{CO}_2$  in the region of these receptors will modify respiration. These receptors are tuned to keep the  $\text{CO}_2$  from accumulating in the tissues.

Similar adjustments can be shown to exist with regard to  $\text{O}_2$ , except that the adjustments here are to prevent  $\text{O}_2$  depletion in the tissues. The adjustments for  $\text{O}_2$  are not so fine because  $\text{O}_2$  diffuses much more slowly than  $\text{CO}_2$ , and for the same reason there is a greater time lag.

In considering these integrations one must bear in mind the following: (1) that the body has a large capacity to buffer  $\text{CO}_2$ , (2) that changes in circulation and respiration modify one another in mechanical ways, and (3) that respiratory adjustments are for the body as a whole whereas circulatory adjustments are summations of local actions in various organs.

The author then discussed changes in blood flow and blood pressure during the respiratory cycle, pointing out that within certain limits these do not modify the blood flow per minute. He next elaborated on the local control of blood flow in tissues. He next brought out the view of Heymans\* that receptors which start the reflexes to adjust respiration are located in the aortic and carotid sinus regions where end-organs are located which also reflexly regulate the circulation. The evidence pro and con for this view is presented. This masterful presentation is concluded with a discussion of the rôle played by the higher nervous centers located in the hypothalamus. The present accumulation of evidence points to the sub- and hypothalamus rather than the medulla oblongata as the regions which may play the dominant rôle in these adjustments.

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\*Edited by Ed. Koch and published by Theo. Steinkopff, Dresden and Leipzig, 1935.

2. Alterations in the Respiratory Mechanism and Their Effects on the Circulation.  
K. F. Wenckebach (Vienna).

The author discussed the comparative physiology of these two systems to show that (1) all the blood must pass through the ventilation chamber before going to the peripheral organs and (2) that the ventilation chamber acts as a suction and force pump for both air and blood. He then reviewed the mechanism of the movements of the thoracic cage. He discussed the various types of respiratory dysfunction and how they are produced (viz., pneumonose, chest deformities and emphysema) and pointed out that these change the normal beneficial action of respiration into a detrimental one. This occurs in part by displacement of the heart and of the diaphragm, by increasing the effort involved in breathing, by decreasing the pumping action of respiration which facilitates the venous return, and by increasing the resistance to pulmonary flow.

3. Pulmonary Circulation in Normal and Pathological States. M. Hochrein (Leipzig).

The output of the right and left ventricle are equal when conditions are stable. The lung vascular-tree is a passive bed that mirrors the disharmonies of the right and left heart. The blood flow is a function of the pressure difference existing between the right ventricle and the left auricle. In fact, pulmonary arterial pressure is the stabilizer of maladjustments in pulmonary flow. There is an optimum rate and depth of respiration as far as blood flow is concerned, deviation from which causes decrease in flow; inspiration augments inflow into the lungs and expiration augments outflow from the lungs.

The lungs normally contain up to one-fourth of the blood in the body. They are one of the blood reservoirs of the body. Increase in intraalveolar pressure decreases the amount of blood in the lung, and a decrease in this pressure has the reverse action. Reflex vasoconstriction of the pulmonary vessels can be demonstrated. Adrenalin normally causes an accumulation of blood in the lungs, but when the lungs are engorged, it has the exact opposite action. Short periods of static effort cause a decrease in the lung blood content, but most exercises of longer duration lead to an increase in lung blood volume which quickly disappears following cessation of the exercise.

While these changes in lung blood content provide for adjustments in gas exchange, they are more important in acting to neutralize any tendency for the output of the right and left heart to become unequal. These changes in lung capacity also operate to permit quick adjustment of the output of the left heart to body needs. Some of these adjustments are of reflex nature. The origin of some of these is in the pulmonary system.

Changes in the pulmonary circulation occur not only in left heart failure, pulmonary sclerosis, emphysema, kyphoscoliosis, but also follow coughing, strain, and asthmatic attacks. The author suggests that sighing respiration may be a compensatory mechanism to accelerate blood flow.

Damage to the lung vessels can cause edema, and insufficiency of the lung vessel muscles may lead to hypostatic pneumonia. The author suggests that a reflex from the abdominal organs may lead to serious lung engorgement with sudden dyspnea as a result.

Clinically, the state of the lesser circuit can be determined by the degree of cyanosis and tachypnea, by the intensity of the second pulmonic sound, by the presence of catarrh, pulmonary edema, and stasis in the greater circuit, by the x-ray appearance of the lungs, and more quantitatively, by the vital capacity. Unfortunately, the value of vital capacity measurements is lessened since it requires the conscious co-operation of the patient.

Luminal in man and barbiturates in animals seem to lessen shock following pulmonary embolism. The author believes that artificial respiration, as with the Drinker machine, is beneficial in convalescing patients, and he recommends in these cases stimulation of the respiratory center.

#### 4. Functional Structure of the Lung Vessels. A. Benninghoff (Kiel).

There is a sphincter at the mouth of the pulmonary artery where it joins the right ventricle. This is the homologue of the bulbus musculature. In man there are no purely muscular type of pulmonary arteries such as constitute the peripheral arteries in the systemic circuit. The pulmonary arteries are either of the easily distensible elastic type or the precapillaries. The former arteries have a system of elastic and muscular fibers so arranged that the muscles act on the elastic strands and vice versa. The alterations in the muscle fibers prevent the vessel wall from acting as a pure elastic body. In this way the vessels are kept from overdistending. The architecture is different in other mammals. He was unable to find ampule formation or arteriovenous shunts in the lung capillary bed.

The veins have more circular muscles than the arteries. In some mammals the veins have also been found to contain cardiac muscles which suggests active contractions.

#### 5. The Resistance of the Lung Circulation and the Mechanisms of Its Regulation. R. Wagner (Breslau).

In animals with chest closed an electric transmission manometer shows that the maximum pressure in the right ventricle is higher during inspiration than expiration. Anything causing stretching of the lungs causes an effect similar to inspiration, presumably by increasing the pulmonary resistance. Vasomotor influences also affect pulmonary resistance. These changes in resistance are buffered by variations in the number of capillaries open. There is thus a reserve of unopened capillaries which vary from time to time.

#### 6. Acute Cardiac Pulmonary Edema. F. Schellong (Heidelberg).

Acute cardiac pulmonary edema occurs in mitral stenosis, but it is particularly common in hypertension and left heart failure. Hindrance to pulmonary onflow following left heart failure is not the only cause. The author states that nervous factors and the amount of blood entering the lungs play important rôles. These combine to cause overfilling of the lung vessels and thus lead to lung edema.

In mitral stenosis congestion of the lung and hindrance to onflow are constantly present so that edema follows readily whenever there is an increase in the amount of blood entering the lungs. Therefore, failure of the right ventricle and venesection by lessening the amount of blood entering the lungs improve the condition. Nitrites act by increasing the splanchnic bed and thus cut down the flow to the right heart. The author states that patients with mitral stenosis can be regarded as feeling vasomotor reactions in their chests. The author believes that digitalis may bring on an attack of pulmonary edema in patients with mitral stenosis and advocates nitrites as a preventive.

Two types of pulmonary edema are found, one occurring in the presence of chronic pulmonary congestion, the other in its absence. The former type occurs at night or following slight effort when the patient is lying down. Dyspnea is an important and dominant symptom and is associated with cyanosis. The treatment is the treatment for congestive failure.

The second type follows rage. It is accompanied by a sense of pressure in the chest, breathing becomes rapid, the patient has no difficulty holding his breath,

and there is no cyanosis. Morphine brings quick relief, as do sedatives and vasodilators. The blood pressure rises in both forms, and the cardiac output increases. The second form, the author believes, is due to nervous reflexes which ultimately lead to the edema of the lungs. The author conceives the elevated blood pressure and increased heart output as the precipitating factors for the attacks. When dyspnea occurs, this sets up a vicious cycle. Nitrites are effective by leading to dilatation of the splanchnic vessels, a decrease return to the right heart and a lowering of the arterial blood pressure.

#### 7. Pneumonose. R. Schoen (Leipzig).

Pneumonose indicates a disturbance of  $O_2$  absorption by the blood resulting from a decrease in the permeability of the alveolar wall. The  $O_2$  tension in the alveoli is normal, and yet the arterial  $O_2$  content is decreased. The author mentions the difficulties of proving the existence of this condition which is inherent in the methods available of obtaining true samples of all the alveoli and of alveolar blood. Clinically, the anoxemia in compensated mitral stenosis with lung congestion may be of this form. There are also forms of toxic origin, particularly those which in a more advanced stage cause pulmonary edema. Interstitial pneumonitis may act as a barrier to  $O_2$  exchange and so may congestion of the alveolar wall.

#### 8. Respiratory Excursion of the Heart and Large Vessels—A Roentgenkymographic Demonstration. G. A. Weltz (Munich).

Respiratory changes in the position of the heart depend on movements of the diaphragm. These changes may be quite marked and cause a marked alteration in heart shadow and so make estimations of heart size very inexact. Usually the heart shadow is found to be decreased in inspiration.

During inspiration, the heart shadow is usually larger than in expiration, and the pulsations of the heart borders are smaller. Respiratory sinus arrhythmia may alter this. The aorta and pulmonary artery move laterally as the heart shadow increases in size. The pulsations of these vessels also vary during the respiratory cycle. In deep expiration the pulsations of the right and left margin of the "aortic" shadow are out of phase. The liver gets less opaque during inspiration.

#### 9. The Activity of the Lung Capillaries. W. Tiemann (Munich).

Not all of the lung capillaries are functioning, some of these being held in reserve. The caliber of the capillaries is determined by the activity of the arterioles and by the state of the alveolar wall. Blood flow is best in inspiration and worst in expiration. However, deep inspiration narrows the capillaries by elongating them. Oxygen, carbon dioxide, adrenalin and histamine have no direct action on the capillaries. The author finds that hypophysin acts on the arterioles. Unlike the systemic capillaries, those of the lung are not actively contractile. These differences may be due to the fact that the blood vessels of the lung serve the body at large rather than the lungs themselves. The lung parenchyma, however, is nourished by the bronchial blood vessels which are part of the systemic circuit and the capillaries of which behave like systemic capillaries.

#### 10. The Dependence of Stroke Volume on Breathing. R. Herbst (Kiel).

The author has used pulse pressure as an index of stroke volume, and his computations suggest that there is cyclic respiratory variation of 15 c.c. during quiet respiration, the stroke volume increase beginning in early inspiration and reaching a maximum early in expiration.

The results are explained as the delayed effect of increased venous return to the right heart as modified by changes in capacity of the lung circuit. The venous return



to the right heart increases in inspiration and decreases in expiration. In deep respiration the differences in output during the respiratory cycle may be greater than 50 c.c.

**11. Relation of Breathing to the  $O_2$  Saturation of Arterial Blood. K. Matthes (Leipzig).**

The author gave a description of a method of determining  $O_2$  saturation in unopened vessels. It involves photoelectric registration of monochromatic light. He used it in the clinic by transilluminating portions of the finger. By using a finger plethysmograph, he can get simultaneous changes in blood volume and so rule out changes in hemoglobin concentration in this part. Histamine is used to give widely dilated capillaries. The author found the ear better suited for  $O_2$  saturation measurement, but it was not feasible to use a plethysmograph for this organ. Instead, he used the transmittability of a green light in the other ear as a control.

In animals a respiratory variation of  $O_2$  saturation was found to occur. The time relation between the onset of inspiration and the rise in  $O_2$  saturation gives an idea of how long it takes for  $O_2$  to get from the air passages to the skin capillaries. This is shortened after exercise. This respiratory cycle fluctuation of  $O_2$  saturation does not occur in normal man. Patients with bronchitis and dyspnea, however, do show respiratory cycle variations in  $O_2$  saturation. Changes in  $O_2$  saturation also occur even in normal persons during speech and hyperventilation.

**12. Vasomotor Influences and Blood Pressure in the Lesser Circuit. A. Strubell-Harkort (Dresden).**

In this polemic and lengthy discussion of the literature the author concludes that there are vasomotor influences.

**13. Respiratory Arrhythmia in Canines. J. Nörr (Munich).**

The author studied 1,000 dogs with chest lead electrocardiograms and determined in each the greatest variation in cycle length during respiration. In the first days of life the heart rate is regular. After a few months, sinus arrhythmia appears and persists up to the ripe age of fifteen years. Fever associated with illness abolishes this arrhythmia. Disease in dogs had no consistent effect on the arrhythmia. Only eight dogs showed extrasystoles and four showed A-V block.

**14. Concerning Respiratory Arrhythmia. A. Schweitzer (Bad Nauheim).**

This study is based on animal experiments. Changes in the degree of sinus arrhythmia can be effected by the action of the carotid sinus reflexes without modifying respiration. The increased tone of the sinus nerve brings out the reflex just as it slows the heart. A good vagus tone is essential for the arrhythmia. The author concludes that the cause for arrhythmia is in part a reflex from the lungs and in part "irradiation" from the respiratory center.

**15. Orthostatic Circulatory Collapse—Gravity Shock Under Reduced Atmospheric Pressures. D. Mateeff (Sofia) and W. Schwarz (Hamburg).**

In reduced atmospheric pressures the capillary bed in the muscles is increased as shown by greater ease with which gravity shock occurs in persons 5,000 meters above sea level than in those at sea level. Mountain sickness disappears when the subject lies down or when the limbs are bandaged when he stands.

**16. The Significance of Respiratory Curves in Different Diseases of the Heart and Large Vessels. A. Luisada (Naples).**

This is a discussion of pneumotachygrams. The author considers that these curves are the resultant of several factors: (a) transmitted impulses from the heart to the chest, (b) movement of the blood out of the chest via the aorta, (c) movement of the blood into the chest via the venae cavae, (d) liver pulsations, and (e) changes in filling of the lung arterial tree.

**17. Significance of Simultaneous Measurements of Venous Pressure and Pulmonary Circulation Time in Cardiac Insufficiency. B. Brusik (Prague).**

These two measurements permit the determination of right- and left-sided failure. In the former the venous pressure rises, and pulmonary circulation time is slowed. In pure left-sided failure venous pressure rises very little, and pulmonary circulation time is unaffected. A grave prognostic sign is an elevation of venous pressure without much change in pulmonary circulation time. For venous pressure the author used the direct method, for circulation time he used decholin. This study is based on observations on 101 patients.

**18. Lung Circulation and Lung Musculature in Atelectasis and Emphysema. E. Reinhardt (Berlin).**

The author claims that narrowing of the capillaries and the venules of the alveolar wall occurs before the onset of inspiration and that their widening occurs before the onset of expiration. Hence, these vessel changes are active. He has not seen empty lung capillaries and can produce changes in lung capillaries by vasomotor stimulation. The lung vessel changes can be produced by stimulating the visceral pleura. He believes that atelectasis is due to a contraction of the lung and bronchial musculature probably following a pleuropulmonary reflex. Emphysema he attributes to a nerve paresis.

**19. Clinical and Experimental Observations on Respiration and Cerebral Reactions During Heart Standstill. P. Formijne (Amsterdam).**

In three patients each Adams-Stokes attack was followed by twitching or apnea. This is attributed to overventilation during heart standstill and transport of this acapnic blood to the brain when the heart beats again. A similar twitching was noted following syncope in one patient. After experimental heart stoppage, apnea occurred regularly and twitching occasionally. Twitching of the muscle seems to require an intact cerebrum. It is not seen in narcosis or coma. While hyperpnea seemed to be the cause of the subsequent apnea, other reflex mechanisms seemed to operate as well.

**20. Silicosis, Respiration and Circulation. G. Brückner (Hamm).**

This is a report of nine cases. Evidence of right heart failure in the venous pulse occurred in early cases and only occasionally in advanced cases. This evidence of failure is a marked systolic collapse and an exaggerated diastolic wave of the venous pulse.

**21. Relation Between "Modality" of Circulatory and Respiratory Disease. S. Koller (Bad Nauheim).**

A statistical analysis is presented showing that when grip is prevalent, the death rate from heart disease is increased, but so is the death rate for those persons without heart disease. In the United States, 30 per cent of those reported dying a respiratory death have circulatory disturbances as a contributing cause.

In Czechoslovakia this is true in only 2 to 3 per cent of the cases. In New York State only 3 to 8 per cent of those dying of circulatory disease have respiratory disease as a contributing cause.

**22. CO<sub>2</sub> and Carbogen in Handling Diseases of the Peripheral Arteries. A. V. di Cio (Buenos Aires).**

In this report 250 c.c. of gas was injected under the skin, the dose being increased daily up to the maximum that the patient will bear (usually 600-700 c.c.). This is used in acrocyanosis and intermittent claudication, apparently, according to the author, with benefit. Carbogen is a mixture of 95 per cent O<sub>2</sub> and 5 per cent CO<sub>2</sub>. A capillary microscope shows an opening up of capillaries and an acceleration of flow. It takes from twelve to sixty hours for these gases to be absorbed.

**23. Respiration Therapy in High Blood Pressure. R. Trumpp (Bad Liebenstein, Thür).**

This report deals with a description of respiratory exercises with purported beneficial results in hypertension.

**24. The Significance of Respiratory Changes in Contour of Electrocardiograms as Evidence of Myocardial Damage. L. Condorelli (Cagliari).**

Respiratory fluctuation of electrocardiographic contour is evidence of vagal action on the heart and coronary vessels. The appearance of respiratory abnormalities may on occasion be the only evidence of myocardial infarction.

**25. The Significance of Selected Leads of Auricular Electrograms in Showing Conduction Disturbances in the Auricles. S. Laufer (Naples).**

Two needle electrodes were used. They were placed in the second and fourth interspaces to the right of the sternum for the right auricle. For the left auricle a urethral catheter arranged with two electrodes was inserted in the esophagus so that the electrodes were at the level of the left auricle. In this way, the author found split and broad P-waves not evidenced in the standard leads.

**26. Experimental Studies Concerning the Meaning of Thoracic Electrocardiograms. R. Schwab (Bad Nauheim).**

An exploring electrode was placed on various regions of the exposed heart of the rabbit which was kept out of contact with the chest, the indifferent electrode being placed in the mouth. No definite characteristic potential field could be obtained on the heart surface. When the heart was surrounded by saline, a definite field was found with one maximum point. When a gelatin cup containing salt solution was placed on the heart, two maxima were found. The author concludes that the two maxima obtained in the closed chest do not depict right and left ventricular activity but rather the edges of the two chambers.

*Ed. Koch* (Bad Nauheim), in discussing this paper, points out its importance in understanding the thoracic lead. This result is in accord with that of Koch-Momms who found two maxima in a single chambered frog heart under similar conditions.

**27. Ligation of the Coronary Veins—Pathological Anatomical Investigations. S. Laufer (Cagliari).**

Following ligation of the coronary veins the author found pericardial fibrosis and in early stages subepicardial hemorrhages, especially in the region of the auricle and interventricular septum. Histologically, he found evidence of stasis in the auricular myocardium within forty-eight hours. This was associated with

subendocardial and subpericardial hemorrhages and with thrombosis of the superficial veins. No such evidence was found in the ventricles. After from fifteen to thirty days there was evidence of cavernous capillary channels in the auricles. The muscles were fragmented and fibroblasts appeared. All this was confined to the auricles. After one year, evidence of auricular fibrosis was discovered. In electrocardiograms negative S-T segments and tall pointed T-waves were found. Perhaps this auricular damage is the cause of auricular fibrillation. Condorelli believes the difference in results between the action on the auricles and ventricles depends on the power of the ventricular contractions to empty the coronary blood via the thebesian channels.

**28. Concerning Pulsatory Movements of Arteries. K. Hürthle (Tübingen).**

The author concludes that pulsatory movement of the arterial wall is the summation of a passive elastic wave which is transmitted at a velocity dependent on the pressure and extensibility of the vessels, and an active wave propagated by muscular contraction.

**29. Strophanthin in Warm-Blooded Animals With Fever. P. Martini and F. Grosse-Brockhoff (Bonn).**

Fever enhances the action of strophanthin. The author determined the relative lethal dose of this drug in rabbits anesthetized with pernocton in which fever was produced by staphylococcus sepsis. The author could not confirm the idea that strophanthin is borne well by patients with fever.

**30. Relation Between Blood Pressure Level and Sulphocyanide Content of Blood. E. Becher, F. Hartner, and E. Herrmann (Frankfort a. M.).**

The authors found no difference in sulphocyanide in "pale" and "red" hypertension patients. In both sulphocyanide concentration is occasionally increased.

**31. The Pressure Distribution Between the Circulation in "Vasa Privata" and "Vasa Publica." H. Havlicek.**

The "vasa privata" are the small lung vessels and "vasa publica" are the large pulmonary arteries and veins. These terms were used by Ruysch in the seventeenth century. The author gives a theoretical discussion of these two parts of the circulation. He emphasizes the importance of arteriovenous shunts.

**32. A New Method of X-ray Examination of Aorta. W. Galli (Maidland).**

The method consists of passing a tube with a condom on the end into the esophagus. This tube is filled with air (120 c.c.) and its position adjusted under the fluoroscope. The throat is anesthetized for this purpose. Even so, some patients cannot tolerate the procedure. This method permits one to see clearly the action of both the descending and ascending aorta in young subjects. In oblique views, one can visualize the ventricles and auricles more clearly.

**33. Observations on the Intact Venous System. A. Schretzenmayr (Cologne).**

The author uses a venous oncometer surrounding the vein which records the volume changes within it. These changes are in part passive and in part active. Various studies show that the latter plays an important rôle.

**34. Experiments to Locate Venous Thrombosis. A. Jäger (Bonn).**

The author found that the following factors are contributory: (1) injury to the vessel wall and (2) changes in the blood flow and an increase in blood coagula-



ventricles into two equal, but in each case different, muscle masses, without strict regard to any anatomic boundaries. The line of transition for Lead I ran almost vertically downward over the anterior surface of the heart and then curved around the apex to extend upward over the posterior surface, being situated on the left ventricle, near its right border in most of its course. The line of transition for Lead III extended along the lateral borders of the heart except inferiorly where it curved over the anterior surface of the left ventricle and interventricular septum.

Rotation of the heart on its long axis did not materially affect the location of these lines of transition with respect to the body. Their position on the heart was changed in proportion to the degree and direction of rotation. These results provide further evidence in support of the view that the duration and contour of the initial deflection of ventricular ectopic beats depend upon the location of the impulse initiation with reference to the hypothetical line of transition for a specific lead and so upon the general direction of the impulse spread in relation to the recording line of that lead. These results further support the view that the contour and duration of the initial complex obtained by stimulation of ventricular sites do not depend wholly upon whether the Purkinje system of one ventricle is excited in advance of that of the other. The level at which the stimulus is applied in reference to the long axis of the body plays but a negligible part in determining the type of complex produced.

AUTHOR.

**Battro, A., and Quirno, N.: Electrocardiogram in Various Congenital Cardiac Abnormalities. Rev. argent. de cardiol. 2: 335, 1935.**

Electrocardiographic changes personally observed in twenty-one cases of congenital heart diseases are here reviewed. The general statement can be made that congenital cardiopathies have no specific electrocardiographic picture. As an exception, in congenital pulmonic stenosis, the following peculiarities may be found quite often: abnormally high P-wave in one or more leads, marked right ventricular preponderance, frequent inversion of T-wave in Leads II and III. About the same characteristics may be found in cases of combined congenital heart diseases, especially in cases of pulmonic stenosis with interventricular communication. In both these conditions, there can be no right ventricular preponderance or even a left one may be found.

In a case of dextrocardia with pulmonic stenosis the right ventricular preponderance was revealed by inverting the electrodes of the arms.

The electrocardiographic findings in congenital heart disease may be summarized as follows: persistence of ductus arteriosus, interventricular communication and Roger's disease, normal electrocardiogram, although either right or left ventricular preponderance may be found in cases of persistent ductus arteriosus. In congenital aortic stenosis there is left ventricular preponderance.

AUTHOR.

**Weber, A.: Cooling and Rheumatism. Ztschr. f. Kreislaufforsch. 28: 190, 1936.**

The author in this theoretical dissertation claims that arteriospasm plays the chief rôle in rheumatic affections, but it does not follow that cooling is the only factor precipitating the spasm. Hyperemia works well in rheumatic affection as long as no irreparable anatomical damage is present. The hyperemia can take the form of warm applications, massages, fever therapy, thyroid preparations, or CO<sub>2</sub> baths.

L. N. K.

Schultz, Mark P.: Cardiovascular and Arthritic Lesions in Guinea-Pigs With Chronic Scurvy and Hemolytic Streptococcic Infections. *Arch. Path.* 21: 472, 1936.

Chronic scurvy and chronic infection with hemolytic streptococci acting synergically may induce nonpurulent carditis in guinea pigs. Valvulitis with fibrinoid degeneration and an intense proliferative reaction constitutes the most prominent lesion. The changes only slightly resemble those seen in cases of rheumatic fever.

For the production of such lesions chronic scurvy at least of mild degree (resulting from a restriction of the vitamin C intake to an equivalent of 6 c.c. of orange juice weekly) is requisite.

Both spontaneous infection with hemolytic streptococci in guinea pigs and that induced in them by inoculation with a strain originally isolated from the lesions of animals with this disease are effective synergically in inducing carditis if their onset does not antedate the development of chronic scurvy, but they are ineffective in this respect if scurvy is induced after a certain degree of antistreptococcic immunity has been established.

Chronic scurvy uncomplicated by infection induces proliferative lesions of minimal extent.

In chronic scurvy of even mild degree there is extensive myositis of the intercostal muscles and of the muscles in the neighborhood of the knee joints. In more severe grades of chronic scurvy slight arthritic changes are demonstrable. These manifestations are apparently unaffected by the presence of infection.

Small localized areas of endocarditis and myocarditis were seen in about half of the control guinea pigs. There were lesions of similar character and distribution in scorbutic and in infected animals, although in the latter they were slightly more extensive and eosinophiles were more frequently present.

Slight aortitis was occasionally noted in all groups of guinea pigs examined. The lesions were apparently not affected by the presence of scurvy, infection, or a combination of the two processes.

AUTHOR.

Leiter, Louis: The Nonspecific Rôle of Pressor Substances in the Plasma of Hypertensive Patients. *Arch. Int. Med.* 57: 729, 1936.

In preliminary experiments the intravenous injection of heparinized plasma of human blood into unanesthetized dogs produced no significant changes in the mean blood pressure, directly recorded. No difference was observed between the effects of plasma from nonhypertensive persons and the effects of plasma from "malignant" hypertensive patients.

The use of the rat as the test animal, to diminish the dilution of the injected plasma by the animal's blood volume, made possible the demonstration of pressor effects from 51, or 44 per cent, of 117 heparinized plasmas.

The distribution of pressor effects of the plasmas among the different clinical groups was independent of the type of hypertension or of the presence of hypertension.

Plasmas from 17 patients with "malignant" hypertension gave no higher incidence of pressor effects or greater rises in blood pressure than plasmas from 100 other subjects, of whom 83 had various types of hypertension and 17 had miscellaneous nonhypertensive conditions.

Plasmas from hypertensive patients did not increase the response of the blood pressure of the rat to minimal effective doses of epinephrine.

As a result of this study and the related work of other investigators, it must be concluded that there is no satisfactory evidence for the theory that "malignant" or "pale" hypertension (or, for that matter, any common form of clinical hypertension) is caused by the presence of pressor substances in the patient's blood.

AUTHOR.

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## Original Communications

### THE USE OF CIRCULATORY MEASUREMENTS IN EVALUATING PULMONARY AND CARDIAC FACTORS IN CHRONIC LUNG DISORDERS\*

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#### INTRODUCTION

THE clinician is not infrequently faced with the problem of differentiating between pulmonary and cardiac insufficiency. The problem presents difficulties unless accessory means are employed to evaluate the genesis of the symptoms presented by the patient.

It is known that the symptoms of pulmonary insufficiency may closely resemble the cardinal symptoms of myocardial failure, i.e., cyanosis, exertional dyspnea, orthopnea, cough, and diminished vital capacity. The accentuated second pulmonic sound also may be a manifestation of either condition. The paroxysmal nature of bronchial asthma often renders it indistinguishable from the asthma that attends left ventricular failure. Even greater confusion arises in those cases in which combined cardiac and pulmonary insufficiency contribute to the pathogenesis of the presenting symptoms. From a diagnostic, prognostic, and therapeutic standpoint, it therefore becomes important in these cases to evaluate the rôle of pulmonary and cardiac factors in the cardiopulmonary derangement. When the clinical picture is not due to pulmonary disease alone, it is also necessary to establish whether the heart failure is secondary to the pulmonary disorder or independent of it.

Clinical methods have failed to give a clear picture of the altered circulatory dynamics in chronic pulmonary disease. Because of its lesser circulatory obligations, the right heart possesses a large physiological factor of safety which enables it to cope adequately with extensive disease of the pulmonary vascular bed. Isolated failure of the right side of the heart may nevertheless occur, and, when it does, this condition is frequently first suspected by the pathologist. Pathological studies, however, have also been unsatisfactory in elucidating

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the effect of chronic lung disorders on cardiovascular dynamics. For example, the finding of right ventricular hypertrophy and dilatation at the post-mortem table does not necessarily imply that the right heart has failed. It may simply mean that the right heart has conditioned itself to the load thrown upon it by the increased pulmonary resistance, this mechanism being analogous to that in essential hypertension in which hypertrophy and dilatation represent similar compensatory adjustments of the left side of the heart to an increased systemic resistance. The application of circulatory measurements has been a real step forward in the attempt to understand the pathological physiology of the heart and circulation in emphysema and other chronic lung disorders. Weiss and Blumgart<sup>1</sup> made pioneer observations in this field. These authors, employing the radium C method, and Tarr, Oppenheimer, and Sager,<sup>2</sup> using the decholin method of studying blood flow through the lungs, observed that in uncomplicated emphysema the rate of circulation through the lungs was within the limits of normal.

Because of these observations this study was undertaken to note the effect of chronic pulmonary conditions upon the circulatory dynamics and to present relatively simple means of differentiating between cardiac and pulmonary insufficiency. Cardiac output determinations were not deemed feasible because such measurements not only require a complicated laboratory set-up, but they postulate normal gaseous exchange. Gas analyses of arterial and venous blood, which are laborious procedures, and vital capacity measurements were not employed in our observations because deviations from the normal would by themselves not have any significant differential value.

*Clinical Material.*—One hundred and two patients with clinical and roentgenographic evidence of chronic pulmonary disease were observed. Of these, 54 cases of bronchogenic (obstructive) emphysema and 16 cases of bronchial asthma were employed as the basis of this communication.

#### METHODS

*A. The Initial Venous Pressure.*—This was determined in an antecubital vein by the direct method of Taylor, Thomas, and Schleiter,<sup>3</sup> modified by moistening the interior of the manometer with 10 per cent sodium citrate.

*B. Right Upper Abdominal Compression.*—Historically, William Pasteur<sup>4</sup> in 1885 seems to have been the first to describe swelling, with or without pulsation, of the jugular vein as the result of pressing upon the engorged liver; he considered this a sign of tricuspid regurgitation. Subsequently Rondot<sup>5</sup> obtained this phenomenon in a variety of circulatory disturbances which we now regard as insufficiency of the right heart; he called it the hepatojugular reflux. Plesch<sup>6</sup> noted the absence of this phenomenon in patients whose right ventricles were still capable of accommodation, and considered the presence of this sign to be of ominous significance. Because this maneuver appeared to be

an additional aid in studying the functional efficiency of the right ventricle, Fishberg and Hitzig<sup>7</sup> employed it in their observations on several hundred patients suffering from a variety of circulatory and noncirculatory conditions. In addition to observing clinically the filling of the cervical veins, they carried out objective measurements of the rise of the venous pressure in centimeters of blood during one minute of sustained right upper abdominal compression. This manometric measurement has definite advantages over simple clinical observations as employed by the older clinicians for the following reasons: First, it is often difficult to judge on clinical grounds the presence of increased distention of the external jugular veins, unless there is manifest failure of the right side of the heart. Second, the clinical method of evaluating the distention of the cervical veins offers difficulties in patients whose external jugular veins are hidden by a thick panniculus or whose veins are excessively prominent or gaping either normally or as a result of phlebosclerosis or other degenerative changes. Third, it permits detection of lesser grades of cervical distention, not grossly demonstrable, and also gives quantitative data for comparative observations. Fourth, it enables registration of a fall of the venous pressure—a phenomenon frequently encountered in normal individuals.

TABLE I  
VENOUS PRESSURE DETERMINATIONS

	INITIAL VENOUS PRESSURE (CM. OF BLOOD)	VENOUS PRESSURE AFTER ONE MINUTE OF R.U.Q. COM- PRESSION (CM. OF BLOOD)
In health	4-8	No rise, or fall of $\frac{1}{2}$ to 2 cm.
In latent or incipient right ventricular insufficiency	4-8-10	1 to 5 cm. rise
In frank right heart failure	Above 8-10	5 to 20 cm. rise

The first column of Table I shows the initial venous pressure measured in an antecubital vein. In normal individuals the venous pressure ranges from 4 to 8 cm. of blood. By pressing over the right upper quadrant for a period of approximately one minute, the venous pressure level in the antecubital vein of normal individuals either remains stationary or eventually falls progressively from 0.5 to 2 cm. provided they breathe as usual and do not tense their muscles. The delayed fall may be explained on the basis of a subsequently diminished venous return due to temporary compression of the inferior vena cava and portal system of veins. In incipient right heart failure, in which the initial venous pressure is either normal or slightly elevated to about 10 cm., a rise of 1 to 5 cm. may occur after one minute of right upper quadrant compression. In frank right heart failure in which the initial venous pressure is considerably above 8 to 10 cm., a rise of 5 to 20 cm. above the original level of venous pressure may be obtained after right upper

quadrant compression. This maneuver is of clinical value since it demonstrates the inability of the right ventricle to take care of the temporary increase of the venous return. It is true that the filling of the cervical veins may be discernible clinically, but these measurements serve to bring out slight disturbances in the functional capacity of the right heart even in the presence of a normal initial venous pressure. That this phenomenon is not merely a "liver" phenomenon, as was regarded by the older clinicians, may be proved by demonstrating similar rises in venous pressure in right heart failure when the left lower quadrant is compressed. This indicates that this so-called liver stasis phenomenon depends primarily upon the elevation of intraabdominal pressure and the resulting increased venous return.

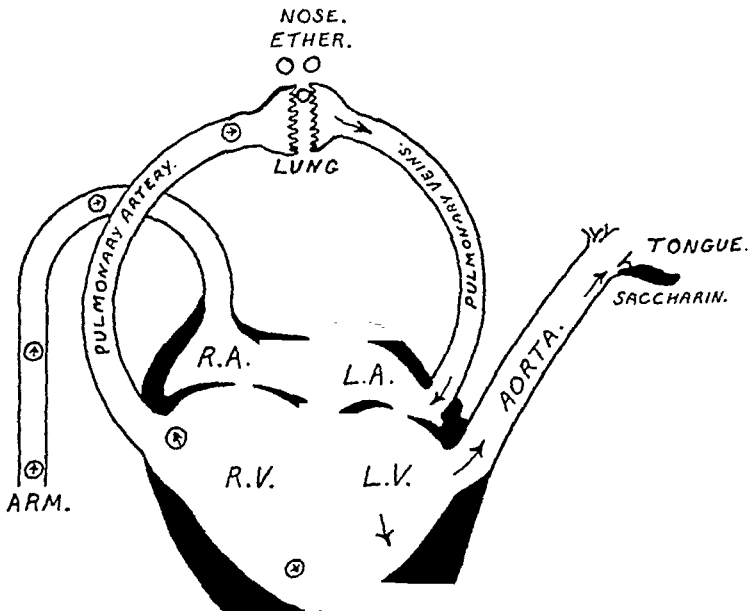


Fig. 1.

C. *Circulation Time*.—1. Arm-to-lung time (ether).

2. Arm-to-tongue time (saccharin or decholin).

3. Lung-to-tongue time (saccharin time minus ether time).

The circulation time from arm to lung is determined by intravenous injection of 5 minims of ether mixed with 5 minims of normal saline. Normally this ranges between 3.5 and 8 sec.<sup>9</sup> The velocity of blood flow from the arm to the tongue is determined by the intravenous injection of saccharin (2.5 cm. in 2.5 c.c. of water) or of 3 to 5 c.c. of 20 per cent solution of sodium dehydrocholate, called decholin.<sup>2</sup> The arm-to-tongue time is normally from 9 to 16 sec.<sup>12</sup> The lung-to-tongue time is determined indirectly by subtracting the ether time from the saccharin time; this is normally between 4.5 and 10 sec. (see Table II and Fig. 1).

The arm-to-lung time may be regarded as a rough measure of the ability of the right heart to maintain a normal velocity of blood flow through its afferent and efferent vessels. The lung-to-tongue time represents a similar function of the left ventricle. Retardation of the rate of flow in the arm-to-lung or lung-to-tongue segments is indicative of functional insufficiency of the corresponding chamber of the heart.

TABLE II

	NORMAL VALUES (SEC.)
Arm-to-lung time (ether time)	3.5- 8
Arm-to-tongue time (saccharin or decholin time)	9.0-16
Lung-to-tongue time (saccharin time minus ether time)	4.5-10

*D. The Blood volume* was determined by the Congo red method in twenty-one patients suffering from emphysema. As it was evident early in the investigation that these determinations offered little of value in differentiating pulmonary from myocardial insufficiency, these measurements were therefore abandoned in the remainder of the series.

*Circulatory Criteria for Determining the Functional Capacity of the Right Ventricle in Chronic Pulmonary Disease (Table III)*

This study was undertaken to determine the presence or absence of circulatory disturbances in patients suffering from varying degrees of

TABLE III

CIRCULATORY CRITERIA OF FUNCTIONAL EFFICIENCY OF RIGHT VENTRICLE  
IN CHRONIC PULMONARY DISEASE

	NORMAL	INCIPIENT ISOLATED RIGHT HEART FAILURE	FRANK ISOLATED RIGHT HEART FAILURE
Initial venous pressure	4-8 cm.	4.5-8 or 10 cm.	Over 10 cm.
R.U.Q. compression	0 or fall	1-5 cm. rise	5-20 cm. rise
Arm-to-lung time	3.5" to 8"	Normal or slight +	+
Lung-to-tongue time	4.5" to 10"	Normal	Relatively normal

pulmonary insufficiency. Although chronic pulmonary disorders may cause hypertrophy of the right ventricle, the so-called cor pulmonale, the functional capacity of this chamber may not be impaired, and the patient suffers from symptoms of isolated pulmonary insufficiency. In these patients, the functional efficiency of the right ventricle is indicated by the presence of the following:

A. A normal venous pressure.

B. The absence of a rise of venous pressure on right upper quadrant pressure.

C. A normal ether time.

In cases, however, in which the peripheral resistance of the lungs is either of long standing or of high grade, slight impairment of the functional efficiency of the right ventricle may be detected by employing two criteria:—

TABLE IV  
BRONCHIOGENIC (= OBSTRUCTIVE) EMPHYSEMA

	I. PULMONARY INSUFFICIENCY ± COMPENSATED COR PULMONALE	II. PULMONARY AND MYOCARDIAL INSUFFICIENCY			
		A. INCIDENT ISOLATED RIGHT HEART FAILURE	B. ISOLATED RIGHT HEART FAILURE	C. LEFT HEART FAILURE ± INCIDENT RIGHT HEART FAILURE	D. UNIVERSAL HEART FAILURE
No. of cases	25	4	7	14	4
Cynosis	17	4	7	12	4
Polycthemia	12	2	3	3	0
Cardiovascular complications	13	0	2	12	4
Acute pulmonary complications	0	0	4	0	1
Initial venous pressure	5 20 0	0 4 0	0 0 7	2 12 0	0 0 4
R.U.Q. compression	{ subnormal normal high	0	0	2	0
		4	7	10	4
Arm-to-lung time	{ no rise of V.P. rise of V.P.	0	0	3	0
		4	7	10	4
Arm-to-tongue time	{ normal prolonged	3	0	9	0
		1	7	5	4
Arm-to-tongue time	{ normal prolonged	4	0	0	0
		0	6	14	4
Lung-to-tongue time	{ normal prolonged	4	6	0	0
		0	0	14	4
Blood volume	{ normal increased	-	1	3	-
		1	1	3	1
Electrocardiogram	{ R.V.P. L.V.P.	3	4	2	0
		0	1	3	0
Deaths	1	0	4	2	2

- A. A rise in the venous pressure on right upper quadrant compression in spite of the presence of a normal or a slightly elevated initial venous pressure.
- B. A normal or slightly prolonged ether time.

When the functional capacity of the right ventricle is grossly impaired, due to extreme reduction of the patency of the pulmonary vascular bed or extreme fatigue of the right ventricular myocardium, a circulatory disturbance which may be regarded as isolated failure of the right heart may be produced. It is noteworthy that in these patients, although there is systemic congestion, there is no congestion in the lungs, the latter condition being characteristically found in disturbances associated with failure of the left side of the heart. The circulatory criteria for frank heart failure of the right ventricle are:

- A. Elevated initial venous pressure.
- B. Marked rise on right upper quadrant pressure.
- C. Prolongation of the ether time except in rare instances.
- D. A normal or relatively normal lung-to-tongue time, the most characteristic finding of isolated right heart failure in contradistinction to right heart failure that follows insufficiency of the left side of the heart.

*Emphysema.*—With these criteria in mind, fifty-four cases of bronchogenic (or so-called obstructive) emphysema were studied. On the bases of clinical features and circulatory measurements, these cases were divided into two distinct groups (Table IV).

1. The first group, which consisted of twenty-five patients, presented no circulatory disturbances. The venous pressure, both initial and after right upper quadrant compression, was normal. The arm-to-lung and the arm-to-tongue times were within normal limits. In addition to the presence of right ventricular hypertrophy demonstrated by x-ray examination and the electrocardiogram, there were also cardiovascular complications in thirteen patients of the series. An important finding in this group is the definite absence of a high venous pressure. In five patients of our series, subnormal venous pressures were actually obtained. In a few cases, showing a marked degree of cyanosis and polycythemia, fast normal circulation times were obtained. This is a significant observation in agreement with the work of Cloetta.<sup>8</sup>

2. The second large group consisted of cases in which pulmonary and myocardial insufficiency coexisted. These cases were subdivided into four groups. The first two groups included cases in which the myocardial insufficiency was secondary to disease of the lung, whereas in the last two groups the heart failure was an incidental complication probably resulting from disease of the left side of the heart. In these latter two groups, when the right heart also failed (incipient or frank failure), it was probably on the basis of marked hypertension of both arms of the pulmonary circuit, due to the combined influence of pulmonary disease and left ventricular insufficiency.

A. Incipient failure of the right heart was observed in four cases. Although these patients presented many of the symptoms and signs of circulatory failure such as cyanosis, orthopnea, and dyspnea, the circulatory measurements were not significantly disturbed. The only consistent abnormality was the presence of a rise of the normal initial venous pressure after right upper quadrant compression. In one case out of the four, there was also retardation of the arm-to-lung time. Otherwise the blood velocity studies were within normal limits. These findings indicate that, although there may be a marked reduction in the cardiac reserve as manifested by the right upper quadrant compression, the other circulatory measurements (venous pressure and circulation times) may be maintained within the normal range.

B. Frank isolated right heart failure was observed in seven patients. In all of these patients many of the characteristic clinical features of right heart failure, such as venous engorgement, enlargement of the liver, cyanosis, ascites, and peripheral edema, were observed. The initial venous pressure was elevated in all cases. On right upper quadrant compression the blood column in the manometer rose from 5 to about 15 cm. above the initial venous pressure level. The arm-to-lung and arm-to-tongue times were prolonged. The lung-to-tongue time, however, fell within the normal range, indicating that slowing of the blood flow was predominantly in the segment between arm and lung. The normal lung-to-tongue time in the presence of a high initial venous pressure and a prolonged ether time appeared to be pathognomonic of isolated failure of the right heart secondary to emphysema.\* This finding is consistent with the absence of pulmonary venous congestion and is indicative of a normal or a relatively better functioning left ventricle. Although there was prolongation of the arm-to-tongue time, there appeared to be no parallelism between the degree of slowing of the blood flow through the lung and the severity of the clinical symptoms, an observation which has previously been made by Blumgart. The symptoms in these patients are probably on a twofold basis: (1) primary disease of the lung,† i.e., pulmonary insufficiency which is the predominant factor, and (2) the slowing of the blood flow through the right heart unit. It is also of interest that in this group four of the seven patients died. In some of these cases death was attributed to right heart

\*It has been suggested that the large amount of residual air in emphysema causes an artificial delay in the passage of ether from the pulmonary capillaries to the nose which may really account for the normal or relatively normal lung-to-tongue time. The latter, which represents the difference between the saccharin and the ether times, is therefore shortened erroneously. This criticism may be refuted by the following observations. First, cases of advanced emphysema, not complicated by right heart failure, yielded normal arm-to-lung times, despite the undoubted presence of excessive residual air. Second, in several instances of severe bronchial asthma, in which a high residual air capacity was undoubtedly present, the arm-to-lung time was normal and almost identical in the acute attack and in the asthma-free interval.

†Under primary disease of the lung are included the secondary effects of the pulmonary disorder upon the patency of its vascular bed, the elasticity of the lung, and the intrapleural pressure. That the resulting decreased negativity of the normal intrapleural pressure plays a rôle in the production of some of the phenomena in pulmonary emphysema has been suggested by the original work of Kountz, Alexander and Dowell.<sup>22</sup>

failure. At post-mortem examination, however, acute bronchopulmonary complications were found. In view of only slight slowing of the circulation time through the pulmonary pathway in these patients, it appears more likely that death was caused by acute increase of the pulmonary insufficiency when the acute bronchopulmonary complication was added to the original condition.

C. Left heart failure with or without incipient right heart failure was observed in fourteen patients. In this group unrelated cardiovascular complications were present in twelve cases and lacking in the remaining two. This finding was probably incidental, inasmuch as many of these patients with emphysema are in the age group where degenerative diseases of the cardiovascular system are prevalent. This classification of the cases with left heart failure was based on the observation of Hitzig, King, and Fishberg<sup>9</sup> in isolated failure of the left ventricle, who found that the venous pressure was normal, that the ether (arm-to-lung) time was usually normal but might be slightly retarded, and that the saccharin (arm-to-tongue) time was usually prolonged. The initial venous pressure in this group was subnormal in two patients, and within the normal range in twelve patients. On right upper quadrant compression, the venous pressure level remained stationary in three patients and rose in ten patients. The arm-to-lung time was normal in nine patients and slightly prolonged in five. The arm-to-tongue time was considerably prolonged in all these patients. The outstanding circulatory disturbance in this group was the presence of consistent prolongation of the lung-to-tongue time. This disturbance was undoubtedly on the basis of left ventricular insufficiency and unrelated to the primary pulmonary disease.

D. Universal heart failure was observed in four patients. All four patients were severely incapacitated. Cardiovascular complications were present in all. The circulatory disturbance probably began with insufficiency of the left ventricle, which, by adding to the burden of an already overstrained right ventricle due to pulmonary disease, led to universal failure of the heart. The initial venous pressure was high in all cases. Right upper quadrant compression caused an enormous rise of the venous pressure level. The arm-to-lung, arm-to-tongue, and lung-to-tongue times were all prolonged. Although the slowing of the blood velocity through the lungs was far greater in this and the previous group than in the group with pure right heart failure, the severity of the clinical symptoms appeared to be no greater in these two groups than in cases due to pure right heart failure (group B).

To summarize the results of circulatory measurements in this group of patients with emphysema, it may be said that, although the right ventricle hypertrophied and dilated in response to the increased work which confronted it in pulmonary emphysema, the circulatory measurements were not prolonged in twenty-five of the fifty-four patients



studied. This is in line with observations of Kountz, Alexander, and Prinzmetal,<sup>10</sup> who concluded that the heart is affected in the majority of patients with emphysema, and that the cardiac lesion, hypertrophy and dilatation of the right ventricle, may produce symptoms, but probably has no clinical reflection in its earlier stages. This work-hypertrophy of the right ventricle may be regarded as the compensated phase of the so-called cor pulmonale. When the work demanded of the right heart exceeds its functional capacity, failure supervenes and gives rise to the so-called decompensated phase of the cor pulmonale. This disturbance was observed in eleven patients of our series. According to the degree of failure and circulatory measurements, we designated four as suffering from *incipient* isolated failure of the right heart, and seven from *frank* isolated failure of the right heart. In eighteen of the patients, who also suffered from combined myocardial and pulmonary insufficiency, the circulatory disturbance probably originated in a majority of instances as a result of unrelated cardiovascular complications which caused either insufficiency of the left ventricle or universal failure.

**Bronchial Asthma (Table V).**—Sixteen patients suffering from bronchial asthma were studied. In all of these patients, emphysema of moderate or marked degree was also present. The circulatory measurements were carried out in all cases during an asthmatic seizure. In twelve of the patients venous pressure determinations were normal; circulation times, however, were either fast normal or average normal. In one of these twelve cases the arm-to-tongue time was even faster than nor-

TABLE V

CIRCULATORY MEASUREMENTS IN ASTHMATIC SEIZURES OF BRONCHIAL ORIGIN  
(INFECTIOUS AND ALLERGIC ASTHMA)

CASE	INITIAL VENOUS PRESSURE (CM. OF BLOOD)	RISE AFTER R.U.Q. COM- PRESSION (CM. OF BLOOD)	ARM-TO- LUNG TIME (SEC.)	ARM-TO- TONGUE TIME (SEC.)	LUNG-TO- TONGUE TIME (SEC.)
1-11	4 to 8	0	4 to 7	8 to 14	4 to 8.25
12	3.5	0.75	5	7.2	2.2
13*	7.5	2.50	8	12.0	4.0
14*	5.5	1.50	4	12.0	8.0
15*	8.0	2.00	7	15.0	8.0
16†	15.5	7.50	12	20.0	8.0

\*Cases showing incipient right heart failure.

†Only case showing frank right heart failure.

CIRCULATORY MEASUREMENTS IN ASTHMATIC SEIZURES OF CARDIAC ORIGIN  
(LEFT VENTRICULAR INSUFFICIENCY)

INITIAL VENOUS PRESSURE (CM. OF BLOOD)	RISE AFTER R.U.Q. COM- PRESSION (CM. OF BLOOD)	ARM-TO- LUNG TIME (SEC.)	ARM-TO- TONGUE TIME (SEC.)	LUNG-TO- TONGUE TIME (SEC.)
6	1	5½	20	14½
8	6	6	28	22
7	4	8	25	17
10	5	9	21	12
7	3	7	24½	17½

mal. In this case when the circulatory measurements were repeated two days after the asthmatic attack had subsided, the results were practically identical with those obtained during the asthmatic seizure. In two other cases, however, the circulation time was faster during the attack of asthma than in the asthma-free interval. Two of these twelve patients died a few days after the normal measurements were obtained; their deaths were apparently due to severe pulmonary insufficiency rather than to heart failure. The necropsy revealed in one case acute suppurative bronchopneumonia, acute putrid and ulcerative bronchitis and cylindrical bronchiectases, and in the second case in which a condition of status asthmaticus prevailed until death, mucous plugs were found occluding all bronchi. Of the remaining four cases, three showed evidence of incipient right heart failure as determined by right upper quadrant compression, and the fourth presented the circulatory dynamics of frank isolated right heart failure, this patient dying two days after the measurements were taken.

*Cardiac Asthma.*—The dyspneic states which frequently accompany chronic bronchopulmonary disease, but particularly bronchial asthma, may closely simulate attacks of cardiac asthma. Although it is well known that paroxysms of wheezing dyspnea in bronchial asthma are primarily due to pulmonary disease with the heart participating only secondarily, because of the increased pulmonary resistance, one often finds it difficult to differentiate these paroxysms from true cardiac asthma in which a pathological process originates in the left side of the heart and involves the lung only secondarily. In spite of the fact that clinical differentiation may frequently be made on the basis of disproportionate cyanosis, secondary polycythemia, the presence of clubbed fingers, a history of allergy and chronic cough, x-ray and electrocardiographic evidence of right ventricular preponderance, this differentiation is not always possible. In such patients, circulatory measurements may be invoked as an aid in the differential diagnosis. This is best exemplified in an analysis of the results obtained in five cases of cardiac asthma, secondary to hypertensive and arteriosclerotic disease of the heart, and also by a comparison of these results with those obtained in bronchial asthma (Table V). The venous pressures were normal in four patients and slightly elevated (to 10 cm.) in the fifth patient. In all patients there was a rise of the venous pressure level of 1 to 6 cm. on right upper quadrant compression. The arm-to-lung time was normal in four, and only slightly prolonged in the fifth case. The arm-to-tongue time, and the lung-to-tongue time were considerably prolonged in all patients. The chief difference between the asthma of bronchogenic and that of cardiac origin is that in the former the circulatory measurements are practically normal, while in the latter there is a consistent rise of venous pressure on right upper quadrant compression and a slowing of the circulation through the lungs exhibited particularly by significant

prolongation of the lung-to-tongue time. However, an occasional case of bronchial asthma associated with heart failure may be observed as is demonstrated in one case (Case 16) in which there was a high initial venous pressure and a rise of venous pressure on right upper quadrant compression. Although the arm-to-lung time was prolonged to 12 seconds, the lung-to-tongue time which was within the normal range, served to differentiate it from true cardiac asthma of left ventricular origin.

*Pneumoconiosis, Silicosis and Pulmonary Fibrosis.*—Circulatory measurements were also carried out in three cases of pneumoconiosis, in one case of severe interstitial fibrosis of both lungs, and in one case of markedly advanced pulmonary silicosis. One may summarize the results by stating that no abnormalities in the circulatory dynamics were recorded in these five cases.

#### COMMENT

The fundamental disturbances in chronic pulmonary disease of the type described in this paper are of twofold nature. One is the altered property of the alveolar walls which interferes with adequate aeration of blood in its passage through the lungs and gives rise to anoxemia. The other is the mechanical reduction in the patency of the pulmonary vascular bed. This latter condition heightens the pulmonary peripheral resistance and leads to a circulatory condition known as hypertension of the pulmonary circuit, which has been popularized by the writings of Moscheowitz.<sup>13</sup> As we shall see later, both of these factors, namely the anoxemia and the pulmonary peripheral resistance, probably play important rôles in the genesis of failure of the right heart in chronic pulmonary disease. Although there is considerable experimental evidence which indicates that the right heart, under ordinary conditions, possesses a large physiological factor of safety, yet instances of isolated failure of the right heart in chronic lung disorders are not infrequently observed. What factors operate in chronic pulmonary disease to cause fatigue and failure of the right ventricle?

The right ventricle performs work in transporting blood through the pulmonary channels to the left side of the heart. The amount of work performed by the right ventricle is determined by the volume of blood it has to propel (venous return) and the pulmonary resistance against which its venous load is ejected. As has been shown by Cloetta,<sup>8</sup> the degree of distention of the lungs also determines in a great measure whether the pulmonary vascular resistance is decreased or augmented. Unless a teleological explanation could be substituted, it is probable that the rapid circulation times in some cases of asthma with emphysema actually result from a reduction in the resistance to blood flow through the lungs. In the majority of instances of emphysema, however, the pulmonary vascular resistance becomes augmented, and the work done by the right ventricular chamber is consequently proportionately in-

creased. As a consequence, even in the early stages of chronic pulmonary disease, the heart may hypertrophy (and even dilate) as a physiological response to increased work. This work-hypertrophy of the right heart, designated in the literature as *cor pulmonale*, enables it to cope adequately with the increased work which confronts it. The circulation through the lungs is thereby maintained at a normal or fast normal speed, and the organism suffers solely from the effects of the primary pulmonary disease and the associated anoxemia.

Recent acute experiments by Fineberg and Wiggers<sup>14</sup> have established a definite relationship between reduction of the functional capacity of the right ventricle and the degree of narrowing of the pulmonary vascular bed. It appears that considerable reduction of the pulmonary vascular bed is necessary before the blood supply to the left side of the heart suffers and arterial pressures decrease. Tigerstedt<sup>15</sup> quotes earlier experiments which indicate that between one-half and two-thirds of the pulmonary branches can be ligated in animals before significant reduction in the mean arterial pressure takes place. Haggart and Walker,<sup>16</sup> and Gibbon, Hopkinson and Churchill<sup>17</sup> found that the lumen of the pulmonary artery could be reduced approximately 60 per cent without reducing the arterial pressure. Recently Fineberg and Wiggers<sup>14</sup> studied the reactions of the right ventricle to graded compression of the pulmonary artery with the aid of optical manometers. By simultaneous registration of right intraventricular and aortic pressures, these authors observed the compensatory reactions of the right ventricle and were able to detect early impairment of left ventricular output when the pulmonary artery was compressed about 58 per cent.

Although sudden drastic reduction in the patency of the pulmonary vascular bed may occur clinically, as for example in massive pulmonary embolization, and give rise to rapid fatigue and progressive failure of the right ventricle, this condition does not appear to be identical with the circulatory derangement that follows long-standing chronic pulmonary disease. In the latter condition right heart failure is probably a gradual summation effect of (a) mechanical overwork and (b) quantitative and qualitative alteration of coronary blood flow. As has been previously pointed out, the long-standing progressively increasing pulmonary resistance leads to a work-hypertrophy of the right ventricle. To maintain its nutrition this progressively enlarging myocardial mass requires a corresponding increase in its blood supply. The coronary circulation is relatively insufficient, quantitatively because of the unchanging and later even diminishing aortic pressures, and qualitatively because of the anoxemia. These factors lead to relative ischemia or anoxemia of the hypertrophying right ventricular myocardium, which in the presence of continued overwork of the right ventricle must eventually lead to its nutritional impairment and to consequent diminution of its functional capacity. It is highly improbable that in these

chronic pulmonary cases, the reduction in the patency of the pulmonary vascular bed ever approaches the critical value that was obtained in the above mentioned acute experiments.

#### SUMMARY

1. Circulatory measurements were employed in the study of pulmonary and myocardial insufficiency in chronic lung disease. The measurements employed were initial venous pressure, the rise of venous pressure during right upper abdominal quadrant compression, the arm-to-lung time (ether), the arm-to-tongue time (saccharin or decholin), and the lung-to-tongue time (saccharin time minus ether time).

2. Uncomplicated pulmonary insufficiency, as is commonly observed in emphysema, is usually attended by normal circulatory measurements, even when associated with right ventricular enlargement.

3. The presence of abnormal circulatory measurements indicates that pulmonary insufficiency is complicated by myocardial failure.

4. The myocardial failure accompanying pulmonary insufficiency is due primarily either to disease of the lungs giving rise to incipient or frank isolated right heart failure, or to unrelated coexisting cardiovascular disorders which result in either left ventricular or universal heart failure.

5. Incipient isolated right heart failure is characterized by the presence of a normal initial venous pressure, and a varying rise in this pressure during right upper quadrant compression. The arm-to-lung time may or may not be prolonged, and the lung-to-tongue time is normal.

6. Frank isolated right heart failure is characterized by high initial venous pressure, considerable rise on right upper quadrant compression, prolongation of the arm-to-lung time and a relatively normal lung-to-tongue time. This indicates that the slowing of the blood flow is confined to the right heart unit, that is, to the segment between the peripheral veins and the pulmonary arterial capillaries.

7. Left heart failure, which may occur as an incidental complication of pulmonary insufficiency, is characterized by normal initial venous pressure with or without a rise on right upper quadrant compression, a normal or slightly prolonged arm-to-lung time, and a considerably prolonged lung-to-tongue time. This indicates that the slowing of the blood flow is largely limited to the left heart unit, that is, to the segment between the pulmonary venous capillaries and the capillaries of the tongue.

8. Universal heart failure, secondary to disease of the left side of the heart and possibly also to coexisting pulmonary disease, is characterized by high initial venous pressure, with a considerable rise in right upper quadrant compression, prolongation of the arm-to-lung time and of the lung-to-tongue time.

9. Bronchial asthma with a few exceptions is characterized by normal initial venous pressure, absence of a rise of right upper quadrant pressure, normal or fast normal circulation times.

10. Cardiac asthma is differentiated from bronchial asthma by the presence of abnormal circulatory measurements, notably by the rise of venous pressure on right upper quadrant compression and by the prolongation of the lung-to-tongue time.

11. That incipient right heart failure also frequently accompanies left ventricular failure may be demonstrated by the method of compressing the right upper quadrant of the abdomen and observing the presence of a rise in the normal initial venous pressure level.

12. In chronic bronchopulmonary disease there is apparently no parallelism between the severity of the clinical symptoms and the slowing of the pulmonary blood flow. Even in those patients who, in addition, present the picture of isolated right heart failure, the clinical symptoms appear out of proportion to the degree of retardation of the circulation through the lungs.

#### REFERENCES

1. Weiss, Soma, and Blumgart, H. L.: Studies on the Velocity of Blood Flow: VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients With Pulmonary Emphysema, *J. Clin. Investigation* 4: 555, 1927.
2. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *AM. HEART J.* 8: 766, 1933.
3. Taylor, F. A., Thomas, A. B., and Schleiter, H. G.: Direct Method for Estimation of Venous Pressure, *Proc. Soc. Exper. Biol. & Med.* 27: 867, 1930.
4. Pasteur, William: A Note on a New Physical Sign of Tricuspid Regurgitation, *Lancet* 2: 524, 1885.
5. Rondot, E.: Le Reflux Hepato-Jugulaire, *Gaz. hebdomadaire de médecine de Bordeaux* 19: 567, 579, 590, 1898.
6. Plesch, J.: In Kraus und Brugsch: Spezielle Pathologie und Therapie Innere Krankheiten 4: part 2, p. 1260.
7. Fishberg, A. M., and Hitzig, W. M.: To be published.
8. Cloetta, M.: Ueber die Zirkulation in der Lunge und deren Beeinflussung durch Ueber- und Unterdruck, *Arch. f. Exper. Path. u. Pharm.* 66: 409, 1911; *Ibid.* 70: 407, 1912.
9. Hitzig, W. M., King, F. H., and Fishberg, A. M.: Circulation Time in Failure of the Left Side of the Heart, *Arch. Int. Med.* 55: 112, 1935.
10. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, *AM. HEART J.* 11: 163, 1936.
11. Kountz, W. B., Alexander, H. L., and Dowell, D.: Emphysema Simulating Cardiac Decompensation, *J. A. M. A.* 93: 1369, 1929.
12. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of Circulation Time With Saccharine, *Proc. Soc. Exper. Biol. & Med.* 30: 651, 1933.
13. Moschowitz, Eli: Hypertension of the Pulmonary Circulation, *Am. J. M. Sc.* 174: 388, 1927.
14. Fineberg, M. H., and Wiggers, Carl J.: Compensation and Failure of the Right Ventricle, *AM. HEART J.* 11: 255, 1936.
15. Tigerstedt, R.: Physiologie des Kreislaufes, Berlin and Leipzig 4: 18, 1923, de Gruyter.
16. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, *Arch. Surg.* 6: 764, 1923.
17. Gibbon, J. H., Jr., Hopkinson, Mary, and Churchill, Edward D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, *J. Clin. Investigation* 11: 543, 1932.

## TRANSIENT AURICULAR FIBRILLATION AS A TOXIC MANIFESTATION OF DIGITALIS\*

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WHILE auricular fibrillation is a common finding in patients with cardiac disease and failure and while digitalis is considered a sheet-anchor in the treatment of such patients, it is uncertain whether or not digitalis in therapeutic doses may bring about auricular fibrillation in patients whose cardiac mechanism was previously normal. A review of the literature reveals that there is no consensus of opinion in this regard and that most authorities do not consider that digitalis may produce auricular fibrillation. Cushny<sup>1</sup> stated: "Auricular fibrillation is said to have occurred under digitalis in cases of previously regular rhythm; in most, perhaps in all, of these cases, careful examination shows that the regular ventricular rhythm is accompanied by auricular flutter; it is not certain that auricular fibrillation is induced by digitalis unless flutter is present before the treatment is initiated." The same author, nevertheless, did produce auricular fibrillation in mammals in the third stage of digitalis action after very large quantities of this drug were injected. Cowan and Ritchie<sup>2</sup> and Lewis<sup>3</sup> in their recent textbooks on heart disease did not mention the possibility that digitalis may produce auricular fibrillation in patients. Robinson<sup>4</sup> studied a case of paroxysmal auricular fibrillation but was unable to draw any definite conclusion as to the influence of the drug on the persistence of the fibrillation. Luten<sup>5</sup> in his clinical studies of digitalis did not encounter auricular fibrillation as a toxic manifestation from his massive doses of digitalis. In a report on transient and recurrent auricular fibrillation, Patterson<sup>6</sup> was unable to show that digitalis was the cause of auricular fibrillation in any of his cases. Cookson<sup>7</sup> and Friedlander and Levine<sup>8</sup> studied the etiology of auricular fibrillation but did not mention the possibility of its precipitation by digitalis.

On the other hand, that digitalis may be responsible for attacks of auricular fibrillation has been suspected by a number of observers. As early as 1910, Mackenzie<sup>9</sup> described a case in a woman with rheumatic heart disease in whom auricular fibrillation appeared with slow ventricular rate at the height of digitalis effect and disappeared four days after the drug was discontinued. Danielopolu<sup>10</sup> reported three cases in which auricular fibrillation followed the administration of digitalis, in each instance the onset of fibrillation occurring coincidently with the maximum digitalis effect. Neuhoff<sup>11</sup> reported a boy with rheu-

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matic heart disease, in whom auricular fibrillation repeatedly appeared at the height of the effect of digitalis; when the drug was discontinued, fibrillation stopped at the end of a day or so. Reid<sup>12</sup> reported two cases, one of hypertensive and the other of syphilitic heart disease, in which partial heart-block and then auricular fibrillation developed after large doses of digitalis. Resnik<sup>13</sup> was perhaps the first who showed definitely that transient auricular fibrillation may follow digitalis therapy. He reported seven patients, five of whom had syphilitic heart disease, in whom digitalization produced auricular fibrillation; in all of these the abnormal rhythm disappeared in from one to six days after the discontinuance of the drug. Resnik advanced the following criteria as the basis for judging whether a causal relationship exists between the onset of auricular fibrillation and digitalis therapy:

1. Absence of history of previous attacks of auricular fibrillation.
2. Normal rhythm before administration of digitalis.
3. Appearance of auricular fibrillation after a dose of digitalis shown by clinical and electrocardiographic evidence to be an effective amount.
4. Persistence of abnormal rhythm as long as digitalis is continued in doses sufficiently large to compensate for the elimination of the drug.
5. Reestablishment of normal rhythm after discontinuance of digitalis.
6. Confirmation of the changes in rhythm by means of electrocardiographic records.
7. Exclusion of other factors which tend to bring on transient auricular fibrillation.

Schwartz and his associates<sup>14</sup> reported on three occasions a total of five cases in children with rheumatic heart disease and heart failure in whom transient auricular fibrillation together with other evidences of digitalis effect in electrocardiograms occurred when digitalis was administered in excessive doses. White<sup>15</sup> stated that, if given in excessive dosage, digitalis may produce auricular fibrillation. McMillan and Bellet<sup>16</sup> reported two cases of hypertensive cardiovascular disease in which auricular flutter was apparently produced by large doses of digitalis. In one of these cases, ventricular tachycardia set in after the onset of auricular flutter, and death soon followed. McEachern and Baker<sup>17</sup> in a study of the etiological factors of auricular fibrillation expressed the belief that in certain instances this rhythm is produced by excessive doses of digitalis. Their study included the five cases previously reported by Resnik and four additional cases, all in patients with syphilitic heart disease. They also referred to a personal communication from Brams and Gaberman, who studied the effect of large doses of digitalis on the electrocardiogram in nine subjects without heart disease and encountered transient auricular fibrillation in one instance (this was not mentioned in the article by Brams and Gaberman<sup>18</sup>).



The author has been impressed by the appearance of auricular fibrillation in patients with heart disease in association with full or excessive digitalization and by its disappearance in these cases on the withdrawal of the drug. In every one of the following 15 cases, all the criteria laid down by Resnik to establish the relationship between the onset of auricular fibrillation and digitalis therapy are met, with the exception of the fourth point, which has been neglected, since it seems unjustifiable to continue digitalis further when auricular fibrillation with slow ventricular rate and frequent ventricular extrasystoles make their appearance. Several cases have been excluded because the relations were not sufficiently clear, or because no electrocardiogram was secured during the attack of abnormal rhythm.

The digitalis used was of standard potency. Assayed on two series of cats on two occasions by Dr. C. Li, of the Department of Pharmacology,\* it gave a potency of approximately 120 per cent in terms of cat units. The apparent lethal doses per kilogram of cat were respectively  $0.083 \pm 0.0028$  gm. and  $0.081 \pm 0.0012$  gm.

#### CASE REPORTS

CASE 1.—A Chinese housewife, aged twenty-seven years, was admitted to the hospital April 27, 1923, for symptoms of congestive heart failure of forty days' duration. Examination revealed cardiac enlargement, mitral stenosis, and congestive heart failure. The cardiac rhythm was regular. The patient was given 1.5 grams of digitalis in two days. On April 30, when the clinical condition improved, the heart rhythm became entirely irregular, and an electrocardiogram revealed auricular fibrillation, flat T-wave in Lead I, inverted T-wave in Leads II and III, and an irregular ventricular rate of about 70 per minute. Digitalis was discontinued. On May 2 an electrocardiogram showed sino-auricular rhythm, P-R interval 0.24 sec., diphasic  $T_2$  and inverted  $T_3$ . On July 5 examination revealed normal mechanism, P-R interval 0.20 sec., and upright T-wave in all leads.

In a patient with rheumatic heart disease, cardiac enlargement, mitral stenosis, and cardiac insufficiency, auricular fibrillation followed the exhibition of digitalis which produced definite clinical and electrocardiographic effects. Both auricular fibrillation and T-wave inversion disappeared on withholding the drug.

CASE 2.—A Chinese male, aged forty-four years, was admitted on three occasions in 1924 and 1925 for congestive heart failure. Blood pressure varied from 194 systolic and 148 diastolic to 224 systolic and 158 diastolic. Cardiac rhythm was regular on the first and at the beginning of second admission on Jan. 12, 1925, when the patient was given 1.7 gm. of digitalis folia in twenty-four hours. On January 14 he developed auricular fibrillation, with alternating ventricular premature beats, and nausea and vomiting. Digitalis was discontinued on January 14. The electrocardiogram on January 20 revealed normal mechanism, with frequent ventricular extrasystoles. Six additional records showed no return of the circus mechanism.

The administration of 1.7 gm. digitalis in twenty-four hours to a patient with hypertensive cardiovascular disease and cardiac failure caused the appearance of auricular fibrillation, with bigeminal ventricular extrasystoles. The circus rhythm reverted to a sinus rhythm six days after the discontinuance of digitalis.

\*The author wishes to acknowledge his indebtedness to Dr. Li for his kind help.

CASE 3.—A Chinese military officer, aged fifty-two years, was first admitted March 1, 1923, for moderate congestive heart failure of short duration. He was found to have syphilis with aortitis and frank aortic insufficiency. The blood Wassermann reaction was strongly positive. Six further admissions took place.

The cardiac mechanism as revealed by repeated electrocardiograms was normal. There was a moderate left axis deviation.

On his last admission, July 13, 1925, owing to his critical condition, large doses of digitalis were given. On the day of admission he received 0.6 gm. of digitalis. The electrocardiogram the next day showed normal mechanism. Digitalis was continued until July 21, when a total of 2.1 gm. was taken in nine days. On that date the electrocardiogram revealed auricular fibrillation, inverted T in Lead I, and low T in Lead II. Digitalis was discontinued on July 23. The electrocardiogram taken July 24 still showed auricular fibrillation, while records on July 27 and August 3 showed sino-auricular rhythm with prolonged P-R interval.

In this patient with syphilis of the cardiovascular system the development of auricular fibrillation was apparently related to digitalis, and reduction in its dosage was followed by reversion to sino-auricular rhythm. The T-wave change and the prolonged auriculoventricular conduction after reversion to sino-auricular rhythm also indicate the effect of digitalis.

CASE 4.—A Chinese man, sixty-four years old, was admitted on Feb. 26, 1930, to the Surgical Service for regurgitation of food for eight months. The findings were essentially normal except for signs pointing to carcinoma of esophagus. The heart was normal; rhythm, regular; blood pressure, normal. There was no venous engorgement. The patient was first operated upon on March 14. On March 18 atelectasis of the left lung was noted, and the heart and the trachea were displaced to the left. The general condition was fair, but the respiratory rate increased to about 23 per minute. With a view to strengthening a displaced heart before the contemplated second operation, which was for excision of the epithelioma, three intramuscular injections of 3 c.c. each of digipuratum at three-hour intervals were given on March 18, and 0.1 gm. of digitalis folia by mouth every day from March 19. On March 19, when the equivalent of 1 gm. had been given, auricular fibrillation and occasional ventricular extrasystoles appeared. On March 21, when patient was receiving 0.1 gm. digitalis per day, the cardiac mechanism reverted to normal, but the T-waves were still flat. The patient died on the operating table March 22.

It appears that the intramuscular injection of 0.9 gm. of digitalis precipitated auricular fibrillation in an elderly man with carcinoma of esophagus but without apparent heart disease or heart failure.

CASE 5.—A Chinese policeman, aged forty-three years, was admitted June 17, 1930, for congestive heart failure for about one month. The history gave multiple venereal exposures in the past. The symptoms became rapidly worse after the onset. The heart was markedly enlarged to the left. There were widened retromanubrial dullness and frank signs of aortic incompetency. The rhythm was regular; edema marked. Both Wassermann and Kahn reactions of the blood were strongly positive.

On admission on June 17 the electrocardiogram revealed normal mechanism and left axis deviation. The patient was given 1.5 gm. of digitalis in twenty-four hours. On June 19 the electrocardiogram showed auricular fibrillation, a slow ventricular rate of about 53 per minute, and diphasic T-waves in all leads. Digitalis 0.2 gm. was given on that day, and 0.1 gm. on June 20; it was omitted from June 21 to 23. On June 24 the electrocardiogram revealed reversion to normal mechanism, low T-waves, and occasional ventricular extrasystoles. Auricular fibrillation recurred on July 31, when marked nausea and vomiting also appeared, after resumption of digitalis. This again disappeared eleven days after the second withdrawal of the drug.

In a patient with syphilis of the cardiovascular system and advanced cardiac failure, full digitalization produced no beneficial response, but apparently brought on auricular fibrillation which disappeared on reducing the dose of digitalis. Slow ventricular rate during auricular fibrillation, inversion of T-waves, and nausea and vomiting support the view that auricular fibrillation was a toxic manifestation of digitalis in this case.

CASE 6.—A Chinese man, aged forty-nine years, was admitted July 15, 1931, for congestive failure for six months. The rhythm was regular, blood pressure, 158/124.

The patient was taking digitalis before admission, when the electrocardiogram showed partial auriculoventricular heart-block (P-R interval 0.24 sec.) and left axis deviation. After admission no digitalis was given for five days. From July 20 to July 27, 1.4 gm. of digitalis were given. On July 28 auricular fibrillation was detected clinically and confirmed by electrocardiogram.

Digitalis was not discontinued, but 0.1 gm. was ordered daily from July 28 to July 31. The electrocardiogram on July 31 revealed transient bigeminal rhythm owing to frequent occurrence of ventricular premature beats, in addition to auricular fibrillation. On August 3, there was auricular fibrillation with bigeminal ventricular extrasystoles. Digitalis discontinued from August 1 to 9. On August 10 the cardiac rhythm was regular again, and a record showed normal mechanism. Owing to the persistence of congestive failure, digitalis was resumed, with 1.7 gm. from August 10 to 20, and 0.1 gm. was given daily from August 12 to 20. The patient developed auricular fibrillation on or about August 19, when the electrocardiogram revealed auricular fibrillation, slow ventricular rate, and bigeminal ventricular premature beats. The patient coughed up fresh blood from August 17 until his death on August 20.

The occurrence of auricular fibrillation, a slow ventricular action, and bigeminal ventricular extrasystoles at a time when one expects a maximum digitalis effect, and their disappearance on withholding this drug, constitute evidence in favor of the view that digitalis caused auricular fibrillation in this patient.

CASE 7.—A Chinese man, aged forty years, was admitted April 28, 1933, for congestive heart failure for two months. He was critically ill, with pulse thready. There was massive effusion in the left pleural cavity with displacement of mediastinum, including the heart, to the right. The liver was enlarged below the costal margin. Three thoracenteses on the day of admission resulted in the removal of 13,100 c.c. greenish yellow pus.

The heart rhythm was regular on admission, when 6 c.c. of digipuratum was administered intramuscularly. On the next day, April 29, 0.6 gm. of digitalis by mouth and 2 c.c. of digipuratum intramuscularly were given in the morning. In the afternoon the ventricular rate suddenly dropped to about 40 per minute, with bigeminal rhythm. The heart rhythm was totally irregular after 5 p.m. An electrocardiogram taken at 8 p.m. on the same day revealed auricular fibrillation, complete auriculoventricular dissociation, bigeminal ventricular premature contractions, and left axis deviation. A second record on May 1 revealed a similar mechanism. Owing to the striking changes in the cardiac mechanism after digitalization, no digitalis was given from April 30 until July 17. Patient's circulatory condition improved gradually. He was discharged in good condition on July 19.

Subsequent records were interesting. On May 2 auricular fibrillation was still present, but not complete auriculoventricular dissociation. There were frequent ventricular extrasystoles of various shapes in Lead II. On May 15, when digitalis had been discontinued for fifteen days, the electrocardiogram first showed reversion to normal mechanism with P-R interval of 0.21 sec.

There is no doubt that in this subject, who suffered from massive pneumococcus pleurisy and whose heart was probably normal, digitalis (1.4 gm. in twenty-four

hours) produced auricular fibrillation, complete auriculoventricular dissociation and bigeminal ventricular extrasystoles. The T-wave inversion also indicates digitalis effect. All these changes disappeared in two weeks as digitalis effect passed off.

CASE 8.—A Chinese man, aged fifty-nine years, was admitted Jan. 12, 1934, for congestive heart failure for about one month. He had been entirely well previously. The patient was orthopneic with marked edema. There were typical central and peripheral signs of aortic insufficiency. The teleradiogram showed a widened aortic arch.

Digitalis 1.2 gm. was given on January 12-13.

An electrocardiogram taken January 13, after 0.6 gm. of digitalis on the day previous and 0.2 gm. on that morning, revealed normal mechanism and left axis deviation. Occasional extrasystoles noted on that day. On January 14 auricular fibrillation with T-wave changes and frequent ventricular extrasystoles appeared. Digitalis was omitted on January 14. From January 15 to 25 the patient received 0.6 gm. of digitalis. After this increase in dosage, the patient developed bigeminal rhythm in addition to auricular fibrillation (confirmed by electrocardiogram). Nausea and vomiting developed January 28.

Digitalis stopped from January 26. On January 30, normal mechanism was restored. Further observations showed that with smaller doses of digitalis, the patient never again developed circus mechanism (last electrocardiogram April 19, 1934).

In a patient with syphilis of the cardiovascular system, digitalis caused the appearance of auricular fibrillation, with bigeminal ventricular extrasystoles, and nausea and vomiting. Sino-auricular rhythm was restored upon reduction of digitalis.

CASE 9.—Patient, a Chinese housewife, aged thirty-four years, was admitted June 28, 1934, for pregnancy near term (para iv) and dyspnea, orthopnea, and cough for one month, and edema of legs for two days. Patient was obese, orthopneic, and cyanotic. The heart was enlarged to left; no murmur; gallop rhythm; blood pressure, 166/120. The abdomen was distended with the gravid uterus.

The electrocardiogram on June 29, the day after admission, revealed normal mechanism, upright T-waves in Leads I and II and inverted T-waves in Lead III. Digitalis medication was begun on June 29, when the patient received 0.8 gm. in divided doses by mouth, 0.7 gm. being given from June 30 to July 2. The electrocardiogram on July 2, after a total of 1.5 gm. in three days, showed still a normal mechanism, low T in Lead I, and diphasic T in Leads II and III. One and two-tenths grams of digitalis were administered from July 3 to 8. Labor started spontaneously on July 6, when delivery by breech presentation occurred. The patient's condition improved after admission, but nausea and vomiting began July 9, when heart rhythm was noted to be totally irregular. Digitalis was omitted on that day, and a record revealed auricular fibrillation, with all T-waves diphasic and the R-T interval deeper than before.

From July 10 on, digitalis therapy was relaxed, only 0.1 gm. per day being given until discharge on August 17. On July 12 the heart rhythm was regular, and a record revealed normal mechanism, auriculoventricular conduction at upper limit of normal (0.20 sec.), and diphasic T-waves in Leads I and II. The patient was last seen on April 20, 1935. The rhythm was always regular in later examinations.

In a patient who had hypertensive disease and cardiac failure precipitated by pregnancy and labor, 2.7 gm. of digitalis in ten days caused marked digitalis effect, as manifested by vomiting and transient auricular fibrillation.

CASE 10.—A Chinese merchant, male, thirty-seven years old, was admitted July 17, 1934, for shortness of breath for two years, cough and swelling of legs and of abdomen for six months. Examination revealed advanced congestive heart failure. The blood pressure was 166/130. The electrocardiogram, July 18, revealed normal

mechanism, low to flat T-waves, and left axis deviation. The patient improved after bed rest and digitalis, and he was discharged on August 3.

After discharge, the patient visited Cardiac Clinic frequently. He took 0.1 gm. digitalis daily from August 3 to 17. From August 18 to 30 he received a total dose of 2.1 gm. of digitalis in twelve days. When seen on September 1, he was very ill. He took 1.2 gm. of digitalis from September 1 to 8, when the patient returned without improvement, and the heart rhythm was noted to be totally irregular. He was readmitted September 9, when the electrocardiogram revealed auricular fibrillation with bigeminal ventricular extrasystoles and flat T-waves. After admission, the patient received no digitalis for six days, and cardiac rhythm returned to normal on September 15. Subsequent administration of digitalis was more cautiously undertaken, with no recurrence of auricular fibrillation.

A patient with hypertensive cardiovascular disease developed auricular fibrillation, with bigeminal ventricular premature contractions, after 3.2 gm. of digitalis in twenty days. Omission of digitalis for six days was followed by return to normal mechanism.

CASE 11.—A young girl, aged fourteen years, was admitted Sept. 27, 1934, for palpitation of heart and dyspnea for several months. The symptoms were suggestive of intermittent claudication of left leg for three months one year ago. She was underdeveloped and undernourished. The heart was enlarged to the right and to the left upper, with findings suggestive of a mitral lesion. No roentgenological evidence of coarctation of aorta was noted. Right brachial arterial pressure varied between 140-170 systolic and 80-98 diastolic. Arterial pulsations were absent in the left arm, over abdominal aorta, and in the lower extremities. The liver was enlarged.

The patient received no medication from admission to October 14. The electrocardiogram on September 20 revealed normal mechanism, tendency to left axis deviation, and upright T-waves. Because of increase of congestive heart failure, the patient was given digitalis in the amount of 3.9 gm. in a period of forty-two days from October 15 to November 26. On November 10 the electrocardiogram showed normal mechanism and a definite lowering of T in all leads.

The digitalis dosage was increased on November 28, as the patient showed no response to treatment. Digitalis 0.8 gm. was given from November 28 to 30. On December 1 the patient developed for the first time nausea and vomiting and, in the afternoon, a "very irregular" heart rhythm for a few hours—no electrocardiogram. From December 1 to 10 digitalis 0.1 gm. was given daily. On December 8 and 10 marked nausea and vomiting were present. Examination showed a totally irregular rhythm, and digitalis was stopped from that date. The electrocardiogram revealed auricular fibrillation, diphasic T in Leads I and II and inverted T in Lead III. The circus rhythm lasted about thirty-one hours. The record on December 12 revealed normal mechanism, but T-wave changes persisted. The patient was discharged improved on December 17. Four days later patient was readmitted in a critical condition. She died with regular sinus rhythm on December 22.

A young girl who had coarctation of aorta and questionable rheumatic heart disease and who was small in stature (height 137 cm. and weight 26 kg.) was probably given somewhat too much digitalis, chiefly on account of her lack of favorable response to the drug. Digitalis seems to have caused transient auricular fibrillation, which disappeared about thirty-one hours after the withdrawal of the drug. Other electrocardiographic signs of digitalis effect were seen.

CASE 12.—A Chinese male, aged fifty years, was admitted Nov. 28, 1934, for congestive heart failure for two months. There were hydrothorax and ascites. The heart was markedly enlarged to the left and there were central and peripheral signs of frank aortic regurgitation.

The electrocardiogram on the day of admission showed normal mechanism, upright T in Leads I and II, and diphasic T in Lead III. Digitalis 1.3 gm. was given from November 28 to 30. Patient became nauseated on November 30, when cardiac rhythm was found totally irregular and a record revealed auricular fibrillation, depressed R-T in Lead II, and inverted T in Lead III. Digitalis was discontinued from November 30 to December 5. The electrocardiogram on December 4 revealed normal mechanism, P-R interval of 0.20 sec., but the R-T interval was still depressed in Lead II and the T-wave inverted in Lead III.

Nausea and auricular fibrillation developed in a patient with syphilitic heart disease after 1.3 gm. of digitalis in two days. Reduction of the dosage resulted in the disappearance of circus mechanism in four days.

CASE 13.—A Chinese housewife, aged forty years, was first seen in the out-patient clinic Oct. 18, 1928, when she had had moderate congestive heart failure for three months. Examination showed mitral stenosis and a regular rhythm. The electrocardiogram before digitalis showed normal mechanism, right axis deviation, upright T in Leads I and II and inverted T in Lead III. The patient was treated successfully for six years in the Cardiac Clinic with digitalis and general measures. Sixteen electrocardiograms during this six-year period all showed normal mechanism. The patient's condition became worse on Nov. 20, 1934, when she was admitted to the hospital. By that day she had received 1.3 gm. of digitalis in seven days. After admission another gram of digitalis was given, a total of 2.3 gm. from November 13 to 24. There was no vomiting prior to admission, but from November 20 on, there were both nausea and vomiting. Auricular fibrillation developed on November 24. The electrocardiogram showed coarse circus waves, a ventricular rate of about 65 per minute, and flat T in Lead I and inverted T in Leads II and III. Digitalis was immediately stopped. Two days later normal mechanism returned, with occasional ventricular extrasystoles. The patient gradually developed uremia and was discharged against advice on November 28. The cardiac rhythm remained regular to the time of discharge.

In a patient with rheumatic heart disease and chronic diffuse nephritis, 2.3 gm. of digitalis in twelve days caused the onset of auricular fibrillation, which reverted to normal mechanism two days after the discontinuance of digitalis.

CASE 14.—A Chinese housewife, aged forty years, was first admitted Feb. 12, 1935, near labor (para ii). A living baby was delivered on February 14. There were cough, shortness of breath, and edema of legs for three weeks. Examination showed cardiac enlargement, mitral stenosis, and moderate congestive failure. The rhythm was regular. The electrocardiogram on February 14 revealed normal mechanism. Digitalis 2.1 gm. was given from February 13 to 25. The general condition improved. Auricular fibrillation developed February 26, from which day digitalis was discontinued. Normal sinus rhythm was restored March 4.

In a woman in labor with rheumatic heart disease, digitalis therapy probably played a rôle in the postpartum production of auricular fibrillation, although it developed several days after the expected time of maximum digitalis effect.

CASE 15.\*—A Chinese man, fifty-seven years old, was admitted twice, first, Jan. 23, 1934, and second, Jan. 20, 1935. On first admission the patient showed signs of moderate congestive heart failure which had been present for eight days. There was no evidence of valvular lesion. The blood pressure was normal. The patient improved after rest and digitalis. The electrocardiogram on Jan. 23, 1934, before digitalis, revealed normal mechanism and upright T-waves in all leads. After 1.9 gm. of digitalis in fourteen days, a second record showed flat T<sub>1</sub> and diphasic T<sub>2</sub> and T<sub>3</sub>. By February 12 patient had received 2.4 gm. of digitalis in twenty-one

\*This case is reported in detail in a separate communication by Dr. C. W. Rien and Dr. K. Y. Ch'in.

days. On that day clinical examination revealed a transient attack of totally irregular heart rhythm, presumably auricular fibrillation, but the irregularity had disappeared several hours later when the electrocardiogram was taken. Besides the T-wave changes similar to those of the second electrocardiogram there was also prolongation of the P-R interval to 0.24 sec.

During the interval between the first and second admissions, the patient visited the Cardiac Clinic regularly. On three or four occasions a low pitched rumbling diastolic murmur was heard at the apex. The patient was constantly under the effect of digitalis during this interval, when his cardiac rhythm was always regular.

The condition became worse in January, 1935, and the patient required admission on January 26. At that time he showed marked dyspnea and orthopnea. The heart was then markedly enlarged. Venous pressure was 250 mm. of blood by direct method.

Patient had received digitalis 11.6 gm. in 109 days up to the day of admission; he was given 0.5 gm. additional on January 26 and 27. He vomited a great deal from January 26 to 28. On January 28 the cardiac rhythm became totally irregular. Digitalis was discontinued for the next two days and an electrocardiogram was taken, which showed auricular fibrillation, flat  $T_1$ , and inverted T in Leads II and III. Because of persistence of congestive failure, digitalis was again administered, 0.5 gm. from January 30 to February 2. Nausea and vomiting increased. Digitalis was discontinued February 3. The electrocardiogram taken on February 4 revealed auricular fibrillation, frequent ventricular premature contractions, sometimes bigeminal in rhythm, and inverted T-waves.

After withdrawal of digitalis, the patient improved gradually. Nausea and vomiting subsided. Cardiac rhythm became regular from February 9. The electrocardiogram on February 13 revealed normal mechanism, sinus bradycardia, and right axis deviation. Cardiac rhythm remained regular until sudden death occurred on March 4, 1935.

Necropsy revealed a myxoma of left auricle protruding into and obstructing the mitral orifice, marked hypertrophy and dilatation of right ventricle, and extensive chronic passive congestion.

In an unusual case of primary myxoma of the heart with apparently normal endocardium and myocardium at autopsy, auricular fibrillation with bigeminal ventricular extrasystoles and other evidences of digitalis intoxication developed during the use of digitalis. On the eighth day after the discontinuance of the drug the mechanism became normal, and remained so until sudden death took place twenty-four days later.

#### DISCUSSION

A careful examination of the foregoing case records and of Table I will leave little doubt that the onset of auricular fibrillation was caused by large doses of digitalis. In Cases 4 and 7 there was no definite evidence of organic heart disease, and the patients suffered respectively from epithelioma of the esophagus and suppurative pneumococcal pleurisy. Digitalis was given in the first case with a view to supporting the circulation before a contemplated major surgical operation in an elderly individual, and in the second case on account of signs of circulatory failure due to marked displacement of the heart. Another case (No. 15) concerned a patient whose heart was normal except for a solitary myxoma of the left atrium, which led to mitral valvular obstruction and to hypertrophy and dilatation of the right side of the heart. In four cases there was frank syphilitic cardio-

vascular disease with aortitis and aortic insufficiency. In all cases the onset of auricular fibrillation was associated with other signs of digitalis effect, such as slow ventricular rate, T-wave inversion, bigeminal rhythm with ventricular premature contractions, and often nausea and vomiting. In all instances the mechanism reverted to normal after the withdrawal (in thirteen cases) or reduction (in two cases) of digitalis. A period of from two to fifteen days (average, five days) elapsed from the time of withdrawal of digitalis to reversion to sinus rhythm. This fairly long period for a marked digitalis effect to wear off is not surprising in view of the previous finding<sup>19</sup> that after moderate doses of digitalis given within a period of eight to twelve hours to a group of patients who were not previously under the influence of this drug, its effects were often still discernible in the electrocardiograms three or four weeks later.

TABLE I

SUMMARY OF FIFTEEN CASES OF AURICULAR FIBRILLATION PRODUCED BY DIGITALIS

CASE NO.	SEX	AGE	DIAGNOSIS	AMOUNT OF DIGITALIS RECEIVED AT ONSET OF AURICULAR FIBRILLATION (GM.)	NUMBER OF DAYS WITHOUT DIGITALIS BEFORE REVERSION TO NORMAL MECHANISM
1	F	27	Rheumatic, mitral stenosis	1.5 in 48 hr.	3
2	M	44	Hypertensive	1.7 in 24 hr.	6
3	M	52	Syphilitic, aortic incompetency	2.1 in 9 days	3
4	M	64	Epithelioma of esophagus, preoperative	1.0 in 24 hr. (0.9 intramuscular)	2 (Had 0.2 gm. during this period)
5	M	43	Syphilitic, aortic incompetency	1.5 in 24 hr.	3
6	M	49	Hypertensive	1.4 in 8 days (Had unknown amount of digitalis before admission)	9
7	M	40	Pneumococcus suppurative pleurisy	1.4 in 24 hr.	15
8	M	59	Syphilitic, aortic incompetency	1.2 in 24 hr.	4
9	F	34	Hypertensive; parturition	2.7 in 10 days	3 (Had 0.2 gm. during this period)
10	M	37	Hypertensive	3.2 in 20 days	6
11	F	14 (Height 137 cm. Weight 26 kg.)	Congenital, coarctation of aorta	2.0 in 13 days	31 hr.
12	M	50	Syphilitic, aortic incompetency	1.3 in 48 hr.	4
13	F	40	Rheumatic, mitral stenosis	2.3 in 12 days	2
14	F	40	Rheumatic, mitral stenosis; parturition	2.1 in 12 days	6
15	M	57	Myxoma of heart	12.1 in 111 days	6



The mechanism of the production of auricular fibrillation by digitalis is not clear. Resnik<sup>13</sup> believed that the phenomenon was due in some cases to strong stimulation of the vagus nerves but that in most cases it was due to direct action upon the myocardium. In one of Resnik's cases there was a reversion to normal rhythm following the use of atropine. He also believed that myocardial failure was an important predisposing, though not a direct, cause of transient auricular fibrillation.

Lewis and his associates<sup>20</sup> showed that vagal stimulation reduced the absolute refractory period of the dog's auricular muscle beating at rates of about 200 per minute to from one-fifth to one-sixth of its full value. Although the refractory period and its variations in human beings are unknown, it is known that the electric systole (Q-T interval of the electrocardiogram) is shortened by digitalis, not only absolutely but in relation to the cardiac rate.<sup>21</sup> This change speaks for shortening of the refractory period which favors the persistence, if not the onset, of the circus mechanism.

It has been demonstrated by a number of observers that vagal stimulation tends to favor the development of auricular fibrillation.<sup>22</sup> This view had been recently substantiated by Nahum and Hoff,<sup>23</sup> who converted the normal mechanisms of four hyperthyroid patients and ten electrically stimulated cats into auricular fibrillation by the administration of acetyl- $\beta$ -methylcholine chloride. It appears probable, therefore, that vagal stimulation plays an important rôle in the production of auricular fibrillation by digitalis.

As to the direct action of digitalis on the myocardium, it is difficult to state positively its rôle in the production of auricular fibrillation. Lewis<sup>24</sup> found that this direct action of digitalis slowed the conduction and prolonged the refractory period of the mammalian auricle. Cushny<sup>25</sup> showed that one of the main toxic effects of digitalis is to increase the irritability of the myocardium, leading to ectopic beats and to auricular fibrillation. It is possible, therefore, that the direct action of digitalis on the myocardium and its indirect action through the vagi may not oppose each other and that both may be responsible for the development of auricular fibrillation, especially in the presence of other factors which in themselves may excite the onset of circus mechanism, such as myocardial disease and cardiac failure.

It has already been pointed out<sup>17</sup> that the production of auricular fibrillation as a result of digitalization is not a matter of mere academic interest. Although, in general, auricular fibrillation with a rapid ventricular rate is an indication for digitalis, the onset of this rhythm in patients who have received large doses of digitalis constitutes an indication that a toxic effect of digitalis is present. It is possible that the further use of the drug might give rise to ventricular tachycardia

or fibrillation or even irreversible cardiac damage. It appears also true that discontinuance or marked reduction rather than further administration of digitalis gives the best chance for improvement in cardiac efficiency and for reversion to normal mechanism.

#### SUMMARY

In fifteen patients, two without and thirteen with heart disease and congestive failure, full digitalization caused the appearance of auricular fibrillation together with other signs of digitalis intoxication. The abnormal rhythm in all cases disappeared several days after the discontinuance of digitalis.

Under certain circumstances transient auricular fibrillation is a toxic effect of digitalis and its occurrence under these circumstances is an indication for the withdrawal of the drug.

#### REFERENCES

1. Cushny, A. R.: *The Action and Uses in Medicine of Digitalis and Its Allies*, London, 1925, pp. 135, 253.
2. Cowan, J., and Ritchie, W. T.: *Diseases of the Heart*, London, ed. 3, 1935.
3. Lewis, T.: *Diseases of the Heart*, London and New York, 1933.
4. Robinson, G. C.: *The Therapeutic Use of Digitalis*, *Medicine* 1: 1, 1922.
5. Luten, D.: *Clinical Studies of Digitalis*, *Arch. Int. Med.* 33: 251, 1924; 35: 74, 87, 1925.
6. Patterson, R. V.: *Transient and Recurrent Auricular Fibrillation*, *J. A. M. A.* 82: 453, 1924.
7. Cookson, H.: *The Etiology and Prognosis of Auricular Fibrillation*, *Quart. J. Med.* 23: 309, 1930.
8. Friedlander, R. D., and Levine, S. A.: *Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease*, *New England J. Med.* 211: 624, 1934.
9. Mackenzie, J.: *Digitalis*, *Heart* 2: 273, 1910-11.
10. Danielopolu, D.: *Arrhythmie complète chez l'homme provoqué par la digitale: rôle du système modérateur*, *Compt. rend. Soc. de Biol.* 79: 97, 1916.
11. Neuhoﬀ, S.: *Clinical Cardiology*, New York, 1917, p. 63.
12. Reid, W. D.: *Some Toxic Effects of Digitalis*, *J. A. M. A.* 81: 435, 1923.
13. Resnik, W. H.: *Transient Auricular Fibrillation Following Digitalis Therapy, With Observations Upon the Reaction to Atropine*, *J. Clin. Investigation* 1: 181, 1924.
14. Schwartz, S. P., and Weiss, M. M.: *Auricular Fibrillation in Children. Its Relation to Rheumatic Heart Disease*, *Am. J. Dis. Child.* 36: 22, 1928. Schwartz, S. P.: *Ibid.* 39: 549, 1930.
15. Jezer, A., and Schwartz, S. P.: *Auricular Fibrillation as an Early Toxic Digitalis Manifestation*, *J. Pediat.* 5: 811, 1934.
16. White, P. D.: *Heart Disease*, New York, 1931.
17. McMillan, T. M., and Bellet, S.: *Auricular Fibrillation: Some of Its Clinical Manifestations and Its Treatment*, *Am. J. M. Sc.* 184: 331, 1932.
18. McEachern, D., and Baker, B. M.: *Auricular Fibrillation: Its Etiology, Age, Incidence and Production by Digitalis Therapy*, *Am. J. M. Sc.* 183: 35, 1932.
19. Brams, W. A., and Gaberman, P.: *The Effect of Digitalis on the T-wave of the Electrocardiogram. An Experimental Study in Human Beings*, *AM. HEART J.* 6: 804, 1931.
20. Dieuaide, F. R., Tung, C. L., and Bien, C. W.: *A Study of the Standardization of Digitalis. I. A Method for Clinical Standardization*, *J. Clin. Investigation* 14: 725, 1935.
21. Lewis, T., Drury, A. N., and Bulger, H. A.: *Observations Upon Flutter and Fibrillation*, Part 6, *Heart* 8: 83, 1921.

21. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole ("Q-T" Interval) of the Heart, *J. Clin. Investigation* 10: 889, 1931; 11: 1241, 1932.
22. Cushny, A. R.: Irregularity of the Heart and Auricular Fibrillation, *Am. J. M. Sc.* 141: 826, 1911.  
Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exper. Med.* 17: 429, 1913.  
Garrey, W. E.: Auricular Fibrillation, *Physiol. Rev.* 4: 215, 1924.
23. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl- $\beta$ -Methylcholine Chloride, With Observations on the Rôle of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* 105: 254, 1935.
24. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, London, ed. 3, 1925, p. 360.
25. Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, London, 1925, p. 97.

# THE EFFECT OF STELLATE GANGLIONECTOMY ON THE CARDIAC FUNCTION OF INTACT DOGS

AND ITS EFFECT ON THE EXTENT OF MYOCARDIAL INFARCTION AND ON  
CARDIAC FUNCTION FOLLOWING CORONARY ARTERY OCCLUSION\*

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FOR SOME years stellate ganglionectomy was performed by a number of surgeons for the relief of pain in angina pectoris. Others doubted the value of the procedure and even condemned it heartily saying that it not only failed to relieve pain satisfactorily, but predisposed the heart to sudden failure and prevented a person with a diseased heart from receiving warning of overwork. In the last few years, however, several who were opponents of stellate ganglionectomy in cases of angina pectoris have changed their views on both clinical and experimental grounds. The following physiological and pathological experimental studies support the view that stellate ganglionectomy does not predispose a heart suffering from circulatory disturbances to failure but definitely minimizes the ill effects of such changes.<sup>1-8</sup>

## LITERATURE

For present purposes a few of the many excellent clinical résumés of the literature bearing on the question at hand suitably summarize the pertinent facts and theories. It is notable that several early opponents of stellate ganglionectomy as an operative treatment for angina pectoris have changed their views considerably in recent years. Danielopolu, on clinical grounds, and Leriche, on both clinical and experimental grounds, were among those who some years ago felt that motor sympathetic fibers essential to the heart passed through the stellate ganglia, and that their removal was contraindicated because sudden asystole might be precipitated, or the function of the heart might be definitely limited. Cutler, who summarized the literature excellently on several occasions, did not omit to mention Danielopolu's warnings; though he himself adjudged the procedure noninjurious to dogs and beneficial to persons suffering from angina pectoris. More recently Leriche has by both clinical and experimental work found occasion to reverse his previous judgment and feels that stellate ganglionectomy is distinctly beneficial in cases of angina pectoris since the procedure lessens the extent of infarction following coronary closure and offsets any tendency to ventricular fibrillation. Swetlow apparently found injection of the ganglia, from the level of C8 to T7, capable of relieving the pain of angina in many cases and quite harmless.<sup>1-6, 9-12</sup>

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The exact scientific explanation for these various clinical opinions is marred by disagreement regarding the paths and positions of the cell stations of the nerves supplying the heart, and the functions of these nerves. Excellent physiological studies, however, have shown that stellate ganglionectomy has no effect on the cardiac function of dogs and their ability to work. It has been found experimentally that the surface temperature of an infarcted area of heart muscle does not change with removal of the stellate ganglia and stimulation of the sympathetic fibers to the heart produces no rise in temperature. It seems proved that, though motor, cardiotonic, vasodilatory, and sensory fibers concerned in the reflex reactions of the heart are generally supposed in dogs to pass to and from the heart by way of the stellate ganglia, the removal of these structures is without deleterious effect. Such a conclusion is supported by the fact that various chemical and hormonal influences may adequately replace the nervous reflexes of the heart in its various reactions to general bodily activity.<sup>13, 14, 15</sup>

The anatomical data most acceptable as a background for the above findings are briefly as follows: Sensory fibers to do with pain leave the heart in the human by the middle and inferior cardiac nerves, travel caudally from the middle and inferior cervical ganglia to the stellate ganglia and reach the cord by way of white rami from the sympathetic chains, from the level of C7, C8, or T1 to T4, or sometimes further caudad still. In dogs the pain fibers run to the stellate ganglia and to a varying number of the upper thoracic ganglia. Stellate ganglionectomy largely interferes with such fibers. Other sensory fibers, more important to heart function than these, and concerned in three well-known reflex arcs, are, however, left quite intact when the stellate ganglia are removed. The depressor nerves from the region of the aortic arch for the regulation of blood pressure and pulse, the fibers from the venous side of the heart which form the sensory side of the Bainbridge reflex and have to do with the regulation of cardiac filling and pulse rate, and the carotid sinus reflex sensory fibers regulating heart rate do not pass through the stellate or upper thoracic ganglia. Except for some sympathetic efferent fibers of the Bainbridge reflex which pass through the stellate ganglia to the heart, the efferent fibers of these important reflex arcs are also unharmed by stellate ganglionectomy in both human and dog, for the majority of the efferent fibers are carried in the vagus nerves.

The efferent sympathetic cardiac fibers in man arise in the lateral horns of the gray matter in the upper thoracic cord and pass to the heart from the superior, middle and inferior stellate, and several of the upper thoracic ganglia. In the dog they all pass from the stellate ganglia to the heart. It is over such fibers that much disagreement occurs, for they have been credited with quite various morphologies and functions from time to time. At present they are considered as acceleratory and tonic

to the heart and as vasodilatory to its vessels. As mentioned above, chemical substances, notably adrenalin, appear capable of replacing efficiently the functions of these fibers so that their loss is theoretically unimportant.<sup>12, 13, 15-18</sup>

#### METHOD

Leriche tied off various parts of the coronary circulation in dogs that had had, and also in those that had not had, stellate ganglionectomy performed. He examined the hearts at various intervals afterward and, where comparable amounts of coronary supply had been tied off, reported that the smallest amount of infarction was found in the dogs that had had stellate ganglionectomy done the longest time before the ligation. Cannon and others have studied the pulse, respirations, and work ability of exercising dogs and found that stellate ganglionectomy had no effect on these measures of cardiac function. We therefore combined these methods, adding a study of basal and exercise cardiac output since it was found that a fairly delicate test of this function could be made.

It is true that many cases of angina pectoris in the human present no definite obstruction of the coronary arteries at autopsy, that the exact nature of angina pectoris in the human is unknown, and that ligation of coronary vessels does not necessarily parallel the conditions extant in the patient suffering from angina pectoris. But, as pathological studies become more searching, more and more hearts of patients who suffered from angina are found to bear evidence of coronary occlusive changes, and increasing numbers of reports are seen of angina cases which were found during life or at autopsy to have been in reality cases of coronary thrombosis. Further, it is commonly felt nowadays that angina pectoris is due to anoxemic changes in the myocardium in the final analysis. It seemed reasonable, in consideration of these points, to proceed as detailed below.<sup>4-6, 15, 19-26</sup>

Male dogs of as similar size and temperament as possible were trained to run on a treadmill, to cooperate in studies of pulse, respiration, blood pressure, and basal and exercising cardiac output. Five of these dogs, after such studies and under proper anesthesia, had the stellate ganglia along with two to four of the upper thoracic ganglia removed. The previous tests were then rechecked, and, when stable readings were reached, the anterior descending branch of the left coronary artery was tied at about its midpoint. This usually gave an area of epicardial blueness about  $1\frac{1}{2}$  inches in diameter, an area approximately one-quarter of the area of the left ventricle. If the area first tied was not quite large enough, ligatures were placed more proximally on the vessels to give the desired extent of infarction. As hearts in dogs of similar size varied in their measurements somewhat, and as the coronary vessels deviated considerably in their mode of distribution and extent of anastomosis, it was not always possible to be sure that exactly similar areas of heart muscle had been infarcted. Such variations were carefully noted and suitable allowances made. At operation, measurements of the size of the heart and of the area of infarction were taken. When the dog was entirely recovered (and usually in forty-eight hours no evidence of ill effect was present) resting and exercise readings were again taken until it was evident that stable readings were being obtained.



Another five of the dogs, following the usual tests, were subjected to as exactly similar coronary occlusion as possible, no stellate ganglionectomy being done first. When the dogs had sufficiently recovered, the tests were repeated until stable results were obtained.

Ten other dogs that had no cardiac output estimations done were used to test the mortality and morbidity between dogs subjected to coronary closure after stellate ganglionectomy and dogs subjected to similar coronary closure without previous ganglionectomy. These dogs were divided into two groups of five dogs each. The ligature in each case was placed quite close to the origin of the anterior descending branch of the left coronary artery, giving an area of infarction considerably greater than one-quarter of the left ventricle.

The dogs were sacrificed only after many check studies had been done. They were usually observed from four to six months after the last operation. Great care was taken throughout to see that all tests were done as uniformly as possible. The hearts were finally preserved for microscopic study to check the gross measurements of the area of infarction.

Electrocardiograms were taken on many dogs before and after the various procedures, especially after coronary ligature was done, to confirm the presence of infarction.\*

The method is summarized in several typical protocols.

*Stellate Ganglionectomy Prior to Coronary Ligature.*—Dog 3, 1933, a male collie, weight 13 kg. (Table 1).

January, February, March.—Dog trained readily for various tests; and pulse, respiration, blood pressure, basal and exercise cardiac output readings taken repeatedly until fairly level results were obtained. Electrocardiographic readings and heart size by x-ray examination were recorded.

April 3, 1933.—A bilateral stellate ganglionectomy was done through lateral chest wall incisions, three ganglia below each stellate being taken. The course after operation was uneventful. A bilateral Horner syndrome was present.

April, May.—Pulse, respiration, blood pressure, basal and exercise cardiac output studies were repeated until readings were stable. Electrocardiogram and the heart size were again recorded.

May 23, 1933.—The heart was exposed through a left rib-spreading incision. The left marginal artery, which was the first large branch of the left anterior descending ramus, was tied 1 cm. from its origin. An area of cyanosis 1 cm. in diameter developed just distal to the tie. There was a good anastomosis evident between the posterior artery of the left ventricle and branches of the anterior descending branch of the left coronary artery. Two ligatures were placed 2 cm. from the origin of the anterior descending branch of the left coronary artery. An area 2 cm. by 3 cm. turned blue, the area so affected extending from the septum in front to the left marginal artery, and from the region of the tie to the apex. The heart measured 7.5 cm. from apex to base. There was no change in cardiac function noted other than a lack of contractility in the part infarcted. The chest was closed, and there was an uneventful course after operation.

June, July, August, September.—All tests done before stellate ganglionectomy and coronary ligation were repeated. There was no evidence of cardiac embarrassment. There was no change in the size of the heart.

Oct. 10, 1933.—The dog was killed. The heart showed an area of infarction 4 cm. by 2 cm. by 0.5 cm., the greatest measurements being taken. There was marked

\*We wish to thank Miss Elizabeth Lambert, of the Department of Physiology of the Harvard Medical School, for her generosity in making our electrocardiographic studies for us.



TABLE II  
TABULATION OF THE VARIOUS TESTS ON DOG 247. NO STELLATE GANGLIONECTOMY WAS DONE PRIOR TO CORONARY LIGATION WHICH PERMANENTLY ELEVATED THE RESTING CARDIAC OUTPUT, AND LOWERED THE EXERCISE OUTPUT

DOG NO.	W.T. KG.	PULSE RECOVERY		B. P.		RESPIRATIONS RECOVERY		O <sub>2</sub> CON-SUMPTION C.C./MIN.		BLOOD O <sub>2</sub>		ART. VEN. O <sub>2</sub> DIFFERENCE		ART. O <sub>2</sub> C. P.	CARDIAC OUTPUT		E. C. G.	HEART SIZE
		REST	WORK	REST	WORK	REST	WORK	REST	WORK	ART. VEN.	ART. VEN.	REST	WORK		REST	WORK		
247	19	100	180	4-7'		80-150		25	60	7'	147	22.0-18.4	3.6	24.5	3972		June 3 8.0	
						75-140		141			23.6-17.1	6.5		2169				
						75-145		118			23.5-16.7	6.8		1735				
	17.6						98-170		330		18.3-13.4	4.9	24	6734				
							95-168		579		20.8-16.0	4.8		12020				
							98-170		434		17.3-13.4	3.9		11128				
Coronary Ligation June 14, 1933																		
	15.8	95	160	4'		78-140		25	60	4'	157.3	20.5-16.2	4.3	22.8	3658		June 14 June 15 8.0 July 15 8.0	
								184.0			19.0-13.9	5.1		3607				
		90	150	4'		78-140		184.0			17.3-12.0	5.3		3471				
									542		22.4-17.6	4.8				11291		
									442		22.4-12.9	9.5			4652			
									482		18.8-12.5	6.3			7650			
									482		18.1-12.9	5.2				9296		

scarring and thinning in the area involved. Microscopic examination confirmed the extent of the infarcted area and the amount of scarring (Fig. 1).

*Coronary Ligation Without Previous Ganglionectomy.*—Dog 247, 1933, a male terrier, weight 16 to 18 kg. (Table II).

May, June.—The dog trained readily and good readings were obtained for the various tests as noted above.

June 12, 1933.—The heart was exposed through a left rib-spreading incision, and the first branch of the left anterior descending ramus of the left coronary artery

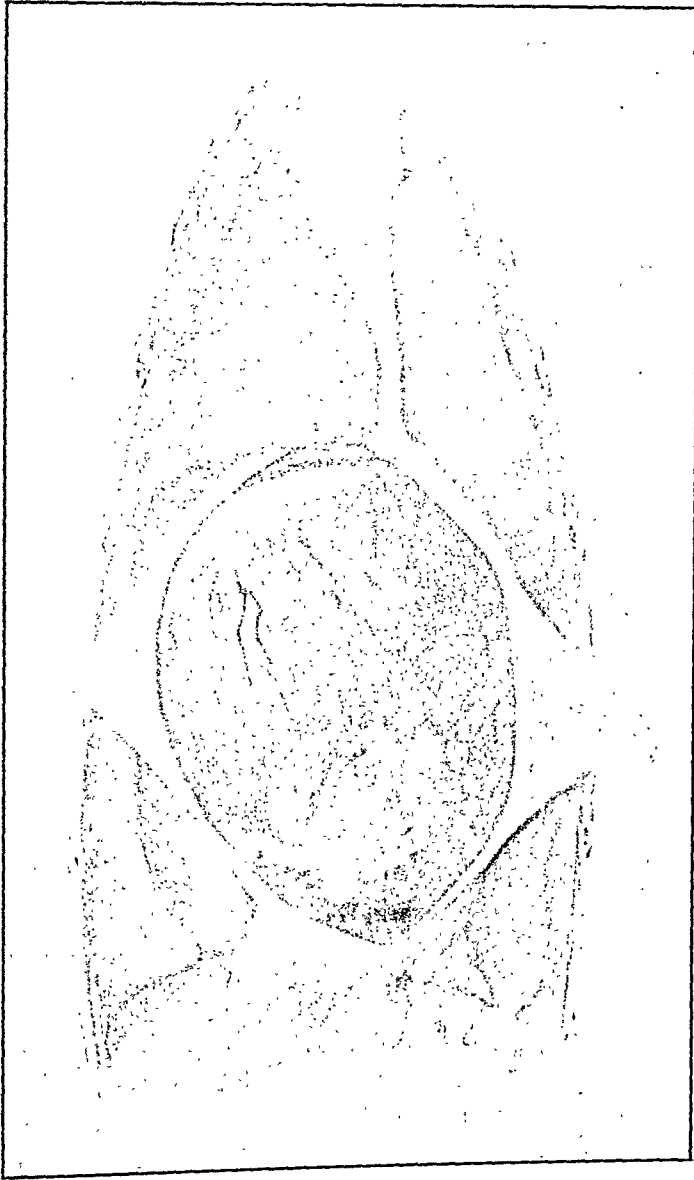


Fig. 1.—A drawing of the heart at autopsy of Dog 3. There was a fair degree of vascular proliferation about the infarct. The stellate ganglia had been removed prior to coronary ligation.

was tied at its origin. Only a small area of cyanosis developed. The ramus itself was now tied about 1 cm. distal to the left auricular tip. An area of cyanosis 2.5 by 1 cm. resulted. The heart measured 6 cm. from apex to base. No change in cardiac function occurred during the procedure other than lack of contractility in the infarcted area. The chest was closed in layers. The course after operation was uneventful.

July, August, September.—The pulse, respirations, and blood pressure were as before operation, but the resting cardiac output remained persistently high while

the exercise output was lowered in nearly every test. The size of the heart did not change.

Oct. 22, 1933.—The dog was sacrificed. An infarct 3 cm. wide was found extending from the apex toward the base of the heart for 5 cm. It was 1 cm. thick. There was marked scarring and thinning of the heart wall in the area of infarction (Fig. 2).

#### OBSERVATIONS

The data regarding pulse, respiration, and blood pressure in the groups with stellate ganglionectomy and without stellate ganglionectomy revealed no marked difference in reaction to coronary ligation either at

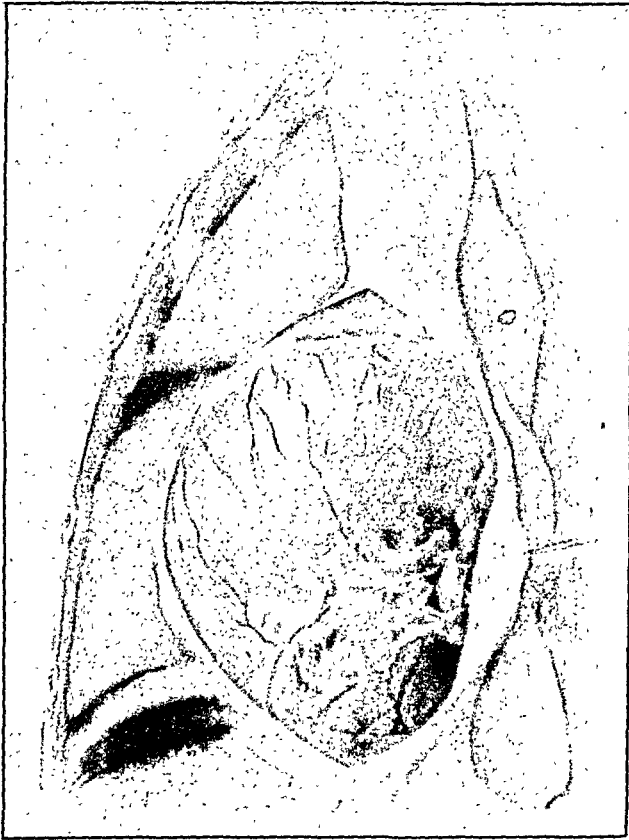


Fig. 2.—A drawing of the heart at autopsy of Dog 247. This dog did not have the stellate ganglia removed before coronary ligation. Some evidence of vascular proliferation was seen about the infarct, but vessels were much less prominent than about the infarct of Dog 3.

rest or during exercise. A very variable elevation of the resting pulse rate was observed in some of the dogs which had the coronary artery tied without previous ganglionectomy. Stellate ganglionectomy by itself produced no change in the resting or exercise readings.

In the ten dogs on which cardiac output estimations were done, a definite difference existed between the five that had stellate ganglionectomy performed prior to coronary ligation and the five that had only coronary ligation. The five dogs that had had no ganglionectomy gave resting cardiac output readings one and a half to twice as high after coronary

TABLE III

TABULATION OF THE VARIOUS TESTS ON DOG 60. NEITHER STELLATE GANGLIONECTOMY NOR, LATER, CORONARY LIGATION MADE AN APPRECIABLE CHANGE IN THE TESTS

DOG NO.	WT. KG.	PULSE RECOVERY REST WORK TIME	B. P. REST WORK	RESPIRATIONS RECOVERY REST WORK TIME	O <sub>2</sub> CON- SUMPTION C.C./MIN. REST WORK	BLOOD O <sub>2</sub> ART. VEN. REST WORK	ART. VEN. O <sub>2</sub> DIFFERENCE REST WORK	ART. O <sub>2</sub> C. P.	CARDIAC OUTPUT REST WORK	E. C. G.	IBI MET SIZE
60/33	13	100 150 2' 90 200 5'	85-135 90-120 80-125	16 28 30 60 5'	199.58 149.75 113.21 373.55 487.23 277.67	19.45-15.36 20.83-11.38 19.52-12.64 15.68-12.29 18.31-14.14 17.93-13.32	4.1 9.5 6.9 3.4 4.2 4.6	20.2 23.7 21.8	5129 1584 1644 10389 11600 6031	Dec. 7 April 7.5	March 7.5
	12.9	Stellate Ganglionectomy									
	15.2	80 150 6'	90-130 90-120 105-165 103-170	20 60 6'	164.0 108.0 185.3 132.9 116.0 540.43 490.8	22.9-16.4 16.5-13.1 22.1-16.3 22.7-17.9 18.2-11.9 20.7-15.9 18.2-14.8	6.5 3.5 5.8 4.6 6.3 4.8 3.4	24.6 26.5	2529 3144 3209 2769 1861 11259 14435	March 30 May 7.5	
	14.2	Coronary Ligation									
		90 170 5'	90-120 80-130 105-175 110-170	30 60 5'	137.9 129.0 177.0 96.8 137.0 162.0 437.0 547.0 402.0	20.7-14.6 22.3-17.5 19.3-13.3 19.4-15.1 18.7-13.4 21.1-14.3 19.5-13.4 22.3-17.5 22.7-19.1	6.1 4.8 6.0 4.3 5.2 6.7 6.1 4.8 3.6	23.4 24.1	2259 2666 2932 2211 2596 2425 7751 11396 11166	June 3 May 7.5 June 7.5 Aug. 7.5	

TABLE IV

Tubulation of the Various Tests on Dog 220. No Stellate Ganglionectomy Was Done Prior to Coronary Ligation Which Permanently Eliminated the Resting Cardiac Output

DOG NO.	WT. KG.	PULSE RECOVERY REST WORK TIME	B. P. REST WORK	RESPIRATIONS RECOVERY REST WORK TIME	O <sub>2</sub> CONSUMPTION C.C./MIN. REST WORK	BLOOD O <sub>2</sub> ART. VEN. REST WORK	ART. VEN. O <sub>2</sub> DIFFERENCE REST WORK	ART. O <sub>2</sub> C. P.	CARDIAC OUTPUT REST WORK	E. C. G.	HEART SIZE
220	15	60 160 4'	95-140	15 40 4'	186.9 184.9 265	20.0-13.9 23.0-15.8 22.0-15.7	6.1 7.2 6.3	24.2	3063 2568 4206	May 20 June 3	May 8 7.0
	14		90-135 95-175 105-170		799 725	18.3-10.9 18.7-12.2	7.4 6.5	22.6	10798 11153		
	Coronary Ligation June 16, 1933										
	13.6	90 170 4'	88-135 86-140	15 40 4'	222 293 258	18.8-14.5 20.2-16.1 16.1-13.5	4.3 4.1 2.6	21.9	5162 7146 9923		June 16 7.0
			103-175 105-170		545 703	22.8-17.7 22.8-17.1	5.1 5.7		10698 12333		July 18 7.0

ligation as before. This increase in resting output declined slightly in a few dogs after several months, but in the others persisted until autopsy four to five months following the operation of coronary ligation. One dog showed a marked decrease in the exercise output while the others showed no remarkable change in exercise output. The five dogs that had been subjected to stellate ganglionectomy showed no change in the cardiac output readings after this procedure, nor was there any change after the coronary ligation was done. These results are summarized in Table V. The figures given in the table for the resting and for the exercise cardiac outputs are not an average of the readings before or after the various procedures but were selected because they appeared to represent most accurately the true cardiac output reading for that particular series of tests from each group of readings. Tables I, II, III, and IV give very representative figures for the various tests on two dogs of each group.

TABLE V

Comparison between typical resting and exercise cardiac outputs, before (B) and after (A) coronary artery ligation, of 5 dogs with stellate ganglia intact, and 5 dogs with stellate ganglia removed

	DOGS WITH GANGLIA INTACT			DOGS WITH GANGLIA REMOVED		
	NO.	CARDIAC OUTPUT		NO.	CARDIAC OUTPUT	
		AT REST	AT WORK		AT REST	AT WORK
B	220	3051	11009	3	1818	13651
A		7164	13799		1872	15214
B	213	2825	14237	119	2810	18487
A		5096	14299		2640	15767
B	247	2169	11116	28	1593	11764
A		3645	7696		2122	11581
B	2	2207	12819	120	2322	13577
A		Fibrillation on ligation			2354	16095
B	260	2765	12803	60	1644	10899
A		Fibrillation on ligation			2259	11254

A comparison of the morbidity and mortality of the dogs which had stellate ganglionectomy done before coronary ligation with those that had only coronary ligation done revealed a striking difference. Ten dogs in all had ganglionectomy done before coronary ligation. They appeared to tolerate myocardial infarction well, only one dying soon after the procedure. The death was apparently due to ventricular fibrillation. The ten dogs, however, that had coronary ligation performed on them, without previous ganglionectomy being done, appeared to be more affected by the operation. Many of the dogs during the first few postoperative days displayed marked cardiac arrhythmia and much more general malaise than those dogs deprived of their stellate ganglia prior to coronary ligation. Moreover, two of the dogs died of ventricular fibrillation immediately after coronary ligation had been done and while

the heart was fully exposed. No accidental factors entered into these deaths, the operations being quite similar to all others done, and other conditions being quite unchanged. Three more dogs died quite suddenly and almost certainly of ventricular fibrillation within a few days of operation. Several of these deaths were witnessed by one of us and were remarkably similar to sudden death from cardiac failure in the human. Table VI summarizes these results.

TABLE VI

Comparison between the tolerance of 10 dogs with stellate ganglia intact, and 10 dogs with stellate ganglia removed, to coronary artery occlusion as evidenced by the incidence of acute cardiac failure following ligation

	DOGS WITH GANGLIA INTACT	DOGS WITH GANGLIA REMOVED
Acute cardiac deaths due to coronary ligation	260 337 213 2 342	320
Dogs healthy after coronary ligation	343 331 247 220 340	299 120 329 324 119 28 302 60 3

A study of the extent of the myocardial infarction in the various hearts following the operation of coronary ligation gave good evidence that ganglionectomy prior to coronary ligation favorably influenced the size of the infarct and its healing. Table VII lists the measurements of the infarcted areas of the various hearts at autopsy. By comparing the hearts from dogs with ganglionectomy prior to coronary ligation, to hearts of similar size from dogs without ganglionectomy prior to coronary ligation, it is seen that in the former the infarcts are invariably smaller. There appeared to be a more vigorous attempt at revascularization in and about the infarcts of the hearts of those dogs that had stellate ganglionectomy done prior to coronary ligation, but no clear-cut decision could be made on this point because of the great variations in the ordinary vascular supply of various hearts. In the group that had had ganglionectomy done prior to ligation, the first procedure had been carried out at various intervals before the second was done, but no definite indication of a difference in the extent of the myocardial infarction in this group of dogs was noted.

The electrocardiographic studies gave the usual evidence of infarction of heart muscle following coronary ligation.

TABLE VII

Comparison between the size of infarct at autopsy of 10 dogs with stellates intact and 10 dogs with stellates removed prior to coronary ligation

DOGS WITH STELLATES INTACT			DOGS WITH STELLATES REMOVED		
DOG	LENGTH OF HEART* (CM.)	SIZE OF INFARCT† (CM.)	DOG	LENGTH OF HEART (CM.)	SIZE OF INFARCT (CM.)
247	6.0	5.5 long 2.5 × 3.0 × 2.0 wide 0.5 × 1.0 × 0.5 deep	299	6.0	4.0 long 2.0 × 3.0 × 2.0 wide 1.0 × 1.5 × 1.0 deep
343	7.0	4.5 long 2.0 × 2.0 × 2.0 wide ? × 0.5 × ? deep	28	6.0	3.5 long 1.5 × 2.0 × ? wide 0.25 × ? × 0.5 deep
213	7.5	4.0 long 2.0 × 2.5 × 0.5 wide 0.5 × 1.0 × 0.5 deep	60	7.0	4.0 long 2.0 × 2.0 × 0.5 wide 0.5 × ? × 0.5 deep
337	7.5	5.5 long 3.0 × 4.0 × ? wide 0.5 × 0.5 × ? deep	3	7.5	4.5 long 2.0 × 2.0 × 3.0 wide ? × ? × 0.5 deep
331	8.0	6.5 long 5.0 × 5.0 × 1.0 wide 2.0 × 1.0 × 1.0 deep	119	7.5	5.0 long 2.5 × 2.5 × 1.0 wide 0.5 × ? × ? deep
260	9.0	5.0 long 4.0 × 4.0 × 1.0 wide 1.0 × 1.0 × 0.5 deep	329	8.5	3.0 long 2.0 × 2.0 × 1.0 wide 1.0 × 1.0 × 0.5 deep
220	9.5	3.0 long 0.5 × 1.5 × 0.5 wide 1.5 × 1.0 × 0.5 deep	120	9.5	3.0 long 1.0 × 1.5 × 2.0 wide 0.75 × 0.5 × 0.5 deep
2	Fibrillation on coronary ligature		320	Acute cardiac failure soon after ligation	
342	Fibrillation on coronary ligature		324	Specimen ill preserved	
340	Animal still alive		302	Specimen ill preserved	

\*Length of heart taken from tip apex to a-v. groove left margin of heart.

†Length of infarct taken as maximum distance from apical end of infarct to basal end of infarct.

Width of infarct measured at 3 points from apex toward base of heart.

Depth of infarct measured at 3 points from apex toward base of heart.

Where measurement is very small "?" is substituted for a figure.

#### DISCUSSION

The above results support the contention of other authors that stellate ganglionectomy is not deleterious to the cardiac function of animals. The results further indicate that stellate ganglionectomy in the presence of coronary closure reduces the incidence of acute cardiac deaths and reduces the size of the resultant infarcts. The question arises as to how far these observations on the effects of deliberate coronary closure in healthy dogs can be applied to human cases of angina pectoris. At least it is fair to say that stellate ganglionectomy is not likely to be in the least harmful to the function of the heart and that, moreover, by cutting the nervous pathways concerned in the pain of angina pectoris, a definite part of the harmful mechanism will be destroyed. The nervous pathways which carry the painful impulses in angina pectoris form a real, and to the patient the most distressing part of the



syndrome; and they may perhaps, as pointed out below, act as a reflex arc which carries pain and other impulses centrally to return impulses to the heart which are deleterious to its function.

Just what sort of deleterious impulses may be carried to the heart over the sympathetic pathways that are connected to the heart through the stellate and upper thoracic ganglia is uncertain. The resting cardiac output of the dogs that had coronary ligation done without previous stellate ganglionectomy became elevated considerably and did not return to a preoperative level. It is possible that the myocardial infarct acted as an irritant stimulating the heart to greater activity through sympathetic overaction. The dogs with stellate ganglia removed prior to coronary ligation did not show any change in the resting cardiac output.

The dogs without ganglionectomy prior to coronary ligation exhibited an increased cardiac output at rest and showed larger infarcts at autopsy than the dogs with the stellate ganglia removed before the coronary ligation. It would appear that the same reflex that caused an increased resting cardiac output caused at the same time a coronary constriction with the production of a large infarct, or at least a lack of vasodilatory reaction about the infarcted area equal to that in the dogs with the stellate ganglia removed. Though it is true that increased cardiac activity usually presupposes an increased coronary flow, the larger coronary vessels do not necessarily dilate. It has not been demonstrated whether the increased coronary flow on cardiac acceleration is due to active arterial vasodilatation or merely to a more rapid flow through the arteriolar and capillary bed of the heart.

Furthermore, since dogs with stellate ganglia intact seemed much more susceptible to acute cardiac failure after coronary closure than dogs with the ganglia removed prior to coronary closure, it would appear that obliteration of the nervous pathways to and from the heart definitely protected the heart from some harmful influence. This circumstance seems comparable to those where spastic lesions in other parts of the body are benefited by section of the sympathetic pathways to the affected part.

The exercise cardiac output was not affected by coronary ligation in either group of dogs. This is accounted for by the fact that only moderate work was used in the exercise tests for reasons given elsewhere. This amount of work was such that the exercise response was not likely to be interfered with by the extent of coronary occlusion used in the experiments.<sup>19</sup>

On the whole it would seem not unfair to conjecture that, far from being a dangerous procedure in angina pectoris, bilateral stellate ganglionectomy or bilateral injection of the lower cervical and upper dorsal ganglia, would not only relieve the pain of angina without being dangerous, but would lessen the mortality of coronary occlusive lesions. It

would eliminate the sympathetic reflex arc, promote vascularization of areas threatened by anoxemia, and allow the heart absolute rest both by the relief of pain to the patient and by elimination of detrimental cardiac reflex responses to myocardial lesions.

#### SUMMARY

Twenty dogs, carefully trained and tested for resting and exercise heart rate, respiratory rate, blood pressure and ten for cardiac output, were subjected to coronary ligation of as similar nature as possible. Half the dogs were subjected, prior to coronary ligation, to bilateral stellate ganglionectomy at which time at least several of the upper dorsal ganglia were also removed.

The dogs with stellate ganglia removed were not affected by this procedure as judged by the above criteria of cardiac function. When coronary ligation was done, there was no change in the cardiac output, heart rate, respiratory rate, or blood pressure. Only one of the ten dogs died of acute cardiac failure. At autopsy the infarcts were all smaller than those found in hearts of similar size in the other group of dogs.

The dogs with stellate ganglia intact were quite definitely much more affected by coronary ligation. There was no great difference between the two groups in pulse, respiration or blood pressure, but resting cardiac output in this group became elevated considerably after coronary ligation and remained elevated. Five of the ten dogs died of acute cardiac failure very typical of the cardiac failure seen in human cases of coronary disease, and all of the hearts of this group exhibited larger infarcts than hearts of similar size in the other group of dogs.

#### REFERENCES

1. Danielopolu, D.: Surgical Treatment of Angina Pectoris, *Brit. M. J.* 1: 180, 1926.
2. Danielopolu, D.: Résultats actuels du traitement de l'angine de poitrine; résultats de 54 cas de suppression du réflexe presseur et de 82 cas de stelléctomie, *Bull. et mém. Soc. méd. d. hôp. d. Bucarest* 14: 297, 1932.
3. Leriche, R., and Fontaine, R.: Surgical Treatment of Angina Pectoris; What It Is and What It Should Be, *Am. Heart J.* 3: 649, 1928.
4. Leriche, R., and Fontaine, R.: Les résultats actuels du traitement chirurgical de l'angine de poitrine, *J. de chir.* 38: 785, 1931.
5. Leriche, R., Herrmann, L., and Fontaine, R.: Ligature de la coronaire gauche et fonction cardiaque chez l'animal intact, *Compt. rend. Soc. de biol.* 107: 545, 1931.
6. Leriche, R., Herrmann, L., and Fontaine, R.: Ligature de la coronaire gauche et fonction de coeur après énérvation sympathique, *Compt. rend. Soc. de biol.* 107: 547, 1931.
7. Iacobovici, I.: Surgical Therapy of 2 Cases of Angina Pectoris by Suppression of Pressor Reflex, *Bucuresti med.* 4: 115, 1932.
8. Braeucker, W.: Die chirurgische behandlung der Angina pectoris, *Arch. f. klin. Chir.* 177: 664, 1933.
9. Cutler, E. C., and Fine, J.: Sympathectomy in Angina Pectoris, *J. A. M. A.* 86: 1972, 1926.
10. Cutler, E. C.: Summary of Experiences Up-to-Date in Surgical Treatment of Angina Pectoris, *Am. J. M. Sc.* 173: 613, 1927.

11. Cutler, E. C.: Present Status of Cardiac Surgery, *Surg. Gynec. Obst.* 54: 274, 1932.
12. Swetlow, G. I.: Angina Pectoris: Paravertebral Alcohol Block for Relief of Pain, *Am. J. Surg.* 9: 88, 1930.
13. Gasser, H. S., and Meek, W. J.: The Acceleration of the Heart in Exercise, *Am. J. Physiol.* 33: Proc. XX, 1914.
14. Sutherland, F. A., Dial, D., and Harris, B. R.: Observations on Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* 30: 1430, 1933.
15. Campos, F. A. deM., Cannon, W. B., Lundin, H., and Walker, T. T.: Some Conditions Affecting Capacity for Prolonged Muscular Work, *Am. J. Physiol.* 87: 680, 1929.
16. Woollard, H. H.: Innervation of Heart, *J. Anat.* 60: 345, 1926.
17. Woollard, H. H., and Norrish, R. E.: Anatomy of Peripheral Sympathetic Nervous System, *Brit. J. Surg.* 21: 83, 1933.
18. Ross, J. P.: Sympathectomy as Experiment in Human Physiology, *Brit. J. Surg.* 21: 5, 1933.
19. Cox, W. V., Hawkins, R., and Robertson, H. F.: A Method of Estimating Both Basal and Exercise Cardiac Output in Dogs, *J. Lab. & Clin. Med.* 21: 192, 1935.
20. Büchner, F.: Die Rolle des Herzmuskels bei der Angina pectoris, *Beitr. z. path. Anat. u. z. allg. Path.* 89: 644, 1932.
21. Büchner, F.: Das morphologische Substrat der Angina pectoris in Tierexperiment, *Beitr. z. path. Anat. u. z. allg. Path.* 92: 311, 1933.
22. Büchner, F., and von Lucadou, W.: Elektrokardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimenteller Coronarinsuffizienz, *Beitr. z. path. Anat. u. z. allg. Path.* 93: 169, 1934.
23. Brow, G. R., and Holman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, *AM. HEART J.* 9: 259, 1934.
24. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
25. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: Electrocardiographic Changes in Myocardial Ischemia, *AM. HEART J.* 6: 522, 1931.
26. Katz, L. N., Mayne, W., and Weinstein, W.: Cardiac Pain; Presence of Pain Fibres in Nerve Plexus Surrounding Coronary Vessels, *Arch. Int. Med.* 55: 760, 1935.

# EXPERIMENTAL EXTRASYSTOLES ELICITED THROUGH ARTIFICIAL STIMULATION OF THE ENDOCARDIUM OF THE DOG\*

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THE generally accepted interpretation of electrocardiograms supposed to represent the activity of the right and of the left ventricle has been subjected during the last few years, to a rigorous re-examination. This reexamination was stimulated chiefly by the work of Barker, MacLeod and Alexander who demonstrated that in man extrasystoles evoked by mechanical stimulation of the cardiac surface do not conform with the generally accepted characteristics of levo- and dextrocardiograms. Fahr, on purely theoretical grounds, had already expressed doubt as regards the validity of the interpretation of bundle-branch block. Oppenheimer and Oppenheimer arrived at similar conclusions as a result of a detailed study of a large number of bundle-branch block cases. These authors succeeded in demonstrating the inadequacy of Lewis' views upon the electrical representation of the left and right side involved in either type of bundle-branch block. Similar to Lewis, who based his views on clinical findings, these authors also based their evidence on clinical and more elaborate anatomicopathological investigation. Wilson, MacLeod and Barker applied a similar reasoning to the interpretation of preponderance curves.

Experimental investigations of the problem were completely disregarded, a fact which is not surprising in view of the divergent results obtained in animal experiments as regards localization by the electrocardiogram of the origin of artificially induced beats. Nevertheless, Roberts and his coworkers brought forward experimental evidence obtained in animals, after transection of one bundle-branch, which is in complete agreement with the results obtained by Barker on man.

As regards the investigation of extra beats no further systematic experimental studies on animals were reported. This is probably due to the fact that the results obtained by stimulation of the surface of the heart are usually not concordant. It is, however, necessary to mention that Barker's findings in man agreed at least with some aspects obtained by Rothberger and Winterberg on animal material.

It is generally accepted that the Purkinje system is the chief source of ventricular extrasystoles. Inducing extra beats by stimulation of the cardiac surface appears, therefore, as a most unnatural method

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for an experimental reproduction of spontaneous extrasystoles. In order to approach conditions which seem to prevail in the case of spontaneous extra beats, I endeavored to evoke extrasystoles in dogs by mechanical stimulation of the inner surface of the ventricular cavity.

Experiments were performed on large dogs, anesthetized with sodium phenobarbital or morphine. The slow heartbeat observed under morphine anesthesia was found helpful in the experiments. The electrocardiogram was taken with the Cambridge string galvanometer in the usual three leads, ordinary plate electrodes being introduced under the skin of the respective limbs. An ordinary Kodak cable release of an appropriate length was used for stimulation purposes. The cable release was introduced into the left ventricle through the carotid artery, and into the right ventricle through the right jugular vein, the thorax of the animal remaining closed. An appearance of sudden irregularities in the blood pressure curve, due to missed beats, indicates that the cable release has reached the ventricular cavity. It is then fixed, by tying a ligature round the respective blood vessel, in such a position that the cardiac contractions again become regular. Once the cable release is fixed, a pressure on its pushpin invariably evokes extra beats, provided that the pin reaches the endocardial surface and provided that the stimulus does not fall into the refractory period. Post-mortem examination clearly reveals the actual point which had been stimulated, as it appears as a pale spot or sometimes as a small blood effusion.

In experiments performed on twenty-six dogs I failed to observe even once electrocardiographic aspects which are usually alleged to represent the corresponding ventricle. Stimulation of the left ventricular endocardium gave rise to an extra beat which invariably displayed in Lead I an electrocardiographic aspect which hitherto has been considered to represent the right ventricular type. Inversely, right ventricular extrasystoles evoked by stimulation of the right endocardium gave in Lead I an electrocardiogram usually regarded as that of the left ventricular type. Lead III showed in the majority of cases a deflection in the direction opposite to that of Lead I, i.e., still displaying characteristics contrary to those which are generally accepted. Sometimes the main deflections in Lead I and Lead III were in the same direction, displaying, therefore, a concordant type and resembling some of the electrocardiograms obtained by Rothberger and Winterberg in epicardial stimulation.

Figure 1 shows a tracing obtained in the dog, in which left ventricular extra beats were evoked by stimulation of the corresponding endocardium. The extrasystoles display a downward deflection in Lead I and diphasic curves in Leads II and III, in the latter case the first Lead III a transition between a definite upward deflection as illustrated by Fig. 3 and a simple downward deflection, sometimes met with when the stimulus proves to have been applied near the apex of the heart. No such variations are presented by Lead I, which invariably shows with endocardially evoked forced beats a main deflection opposite to that which would be expected on the basis of the classical interpretation.

Right ventricular extrasystoles elicited through mechanical stimulation of the right endocardium, as shown in Fig. 2, display an upward directed deflection in Leads I and II and a downward directed main deflection in Lead III. Again, there may be some variations in Lead III, but Lead I invariably shows an electrical deflection which is the reverse of that generally looked upon as representing right ventricular extra beats. It is important to emphasize the constancy of

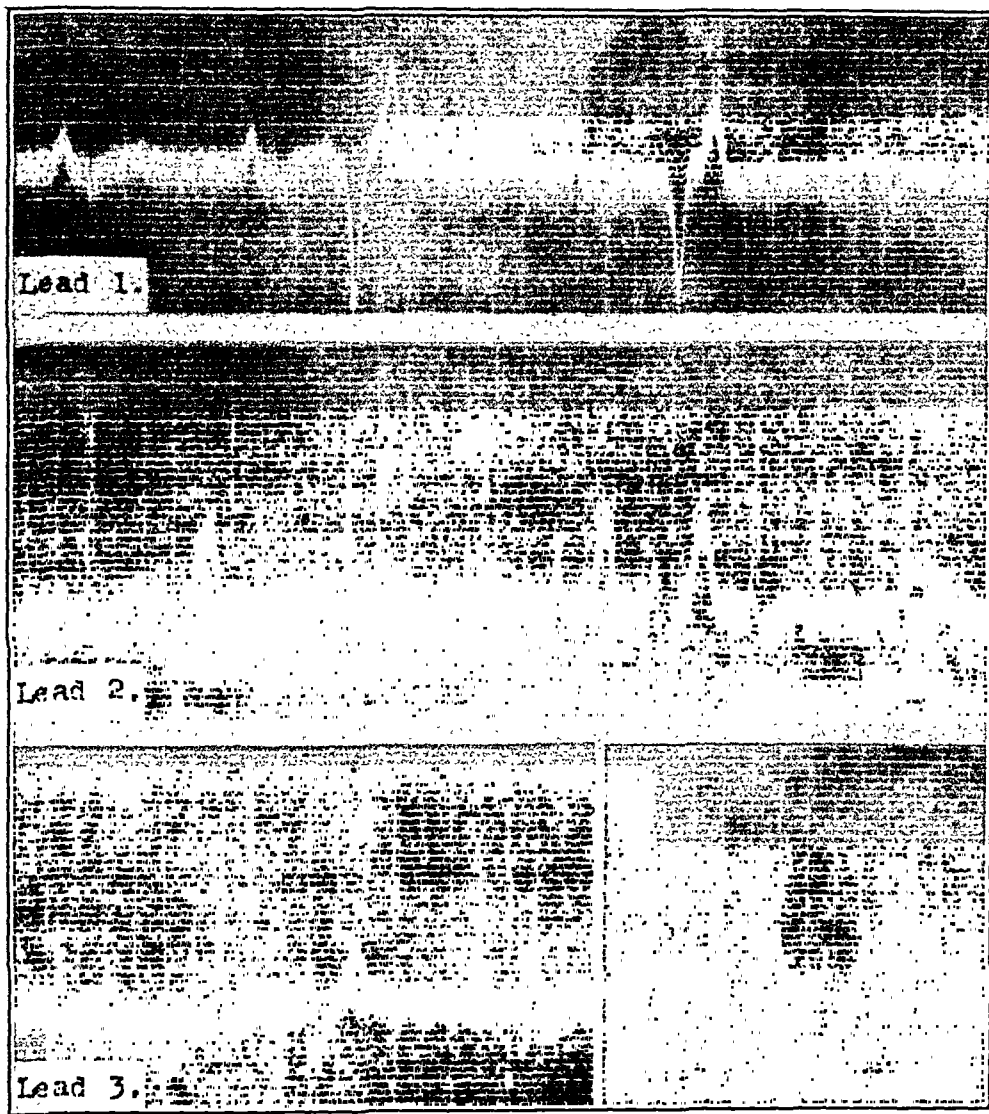


Fig. 1.—Left ventricular forced beats in dog weighing 24 kg. and anesthetized with morphine and phenobarbital. Cable release introduced into left ventricle. Canine electrocardiograms in the usual three leads, with string sensitivity 1 cm. corresponding to 1 mv. Horizontal lining in millimeters, vertical time marking in fifths of a second throughout all figures.

Left ventricular extrasystole of aberrant diphasic type, evoked through mechanical stimulation of the endocardium, interfering with the sequence of normal heartbeats.

the electrocardiographic aspects displayed by the extra beats induced by endocardial stimulation.

In some instances, extrasystoles which are induced by mechanical stimulation of the endocardium are followed by spontaneous extra beats; these display the same electrocardiographic aspect. Fre-

quently, under these conditions, groups of spontaneous extra beats of identical type can be evoked by occlusion of the aorta or by faradic stimulation of the extracardiac nerves. Figure 3 shows left ventricular extrasystoles with a downward deflection in Lead I and an upward deflection in Lead III. The first extra beat in each lead is forced through endocardial stimulation; the second is spontaneous. Both

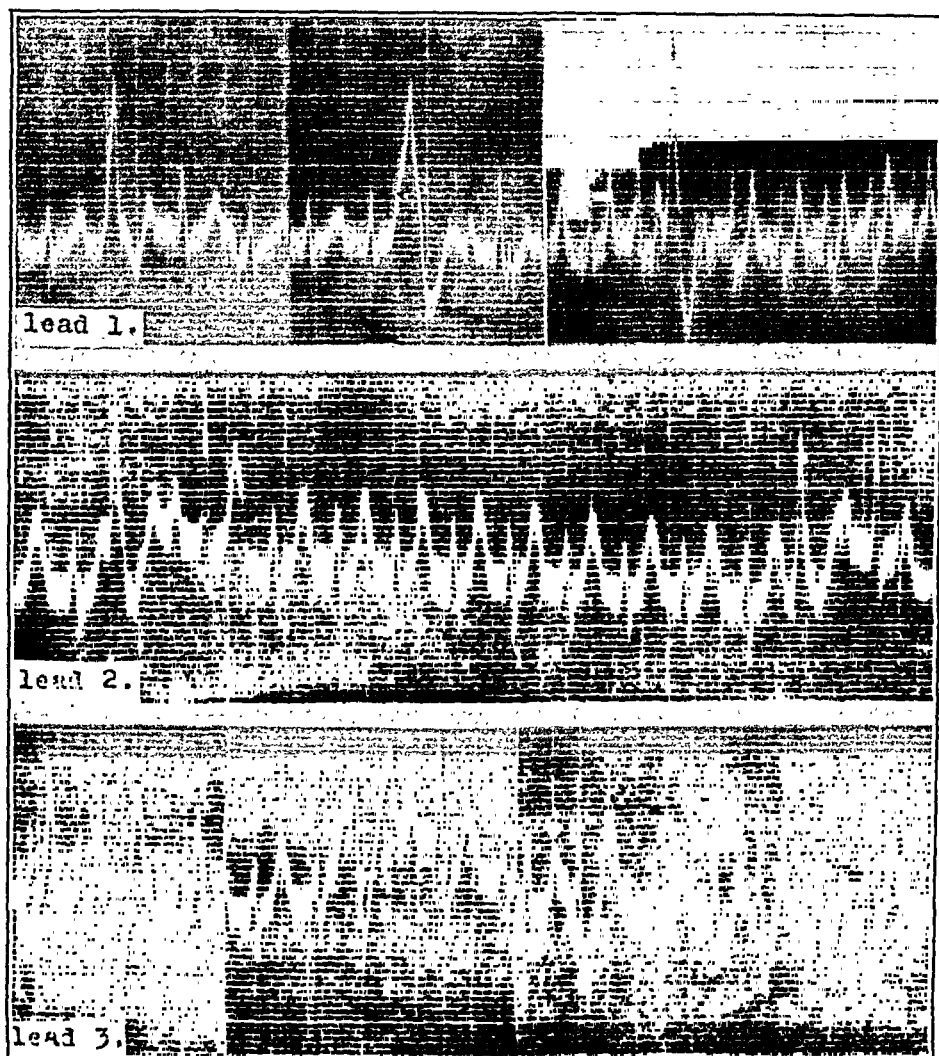


Fig. 2.—Right ventricular extra beats in dog weighing 22 kg. and anesthetized with morphine. Cable release introduced through jugular vein into the ventricle. Right ventricular extrasystole of aberrant diphasic type, evoked through mechanical stimulation of the endocardium, to be seen disturbing the normal rhythm in all three leads.

extra beats display almost identical aspects of their electrocardiographic records. The same happens in the case of right forced and spontaneous extra beats as can be seen from Fig. 4.

It is of interest that in normal animals spontaneous extrasystoles sometimes occur during a temporary occlusion of the aorta, display-

ing an electrocardiographic aspect which is identical with that observed in forced endocardial left ventricular extra beats.

There is a definite discrepancy between my observations and those of Rothberger and Winterberg, made with extra beats of epicardial origin. The following considerations should, however, be taken into account. Lewis has shown that an artificial wave of excitation initiated by stimulation of the cardiac surface, has to penetrate through the whole thickness of the muscle and reach the Purkinje network before it is picked up and conveyed to the whole lining of the heart. Lewis also states that in the case of the thick left ventricular wall the

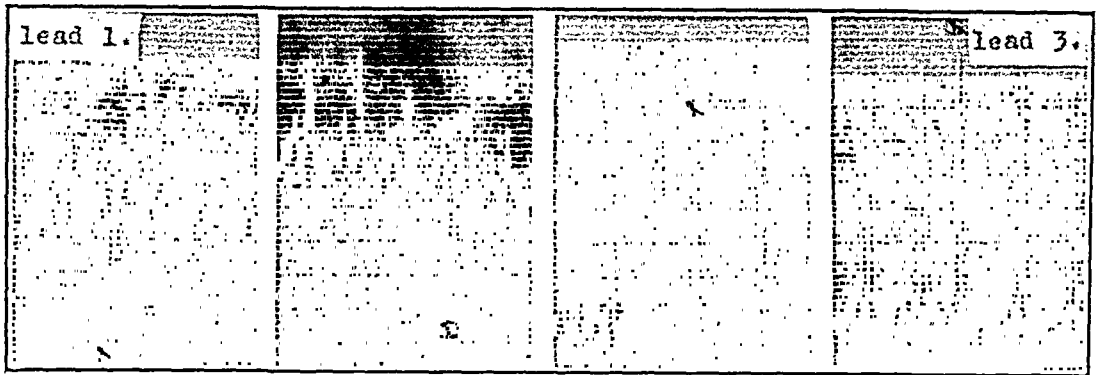


Fig. 3.—Dog weighing 18 kg., anesthetized with phenobarbital anesthesia. Electrocardiograms in Lead I and Lead III.

First premature beat interfering with the normal rhythm in each lead is forced through mechanical stimulation of the inner surface of the left ventricle. The second to be noticed in each lead is spontaneous; note its almost identical aspect.

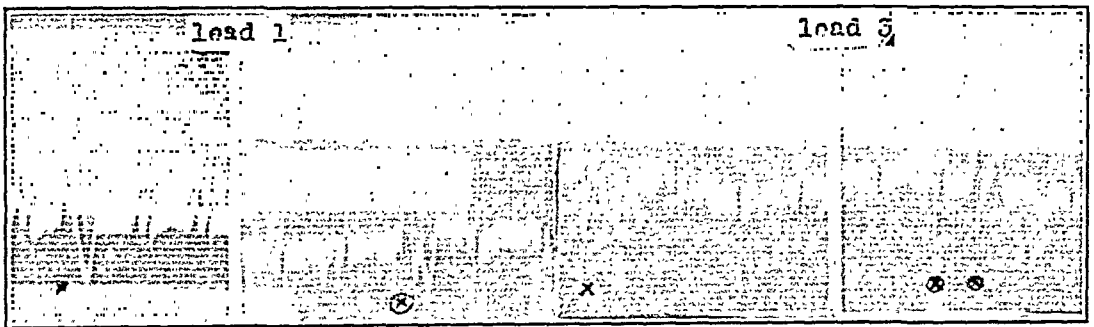


Fig. 4.—Dog weighing 23 kg., anesthetized by phenobarbital. Left group of records in Lead I, right group in Lead III.

First of each displaying an extrasystole elicited through mechanical stimulation of the right ventricular endocardium, the second, a spontaneous extrasystole with similar electrocardiographic aspect.

propagation rate is greater along the surface of the heart than across the muscle itself. Thus an excitation wave initiated by a stimulus which is applied to the surface of the left ventricle at a point not far removed from the interventricular septum may travel along the surface of the heart and penetrate through the thin wall of the right ventricle before it has time to penetrate through the thick wall of the left ventricle, the right Purkinje network being then stimulated first. Experimental support is to be found in the observations made by Wiggers on the spread of impulses originating from artificial heart



surface stimuli. Stimulation of the surface of the left ventricle may thus, in certain cases, evoke a right ventricular extrasystole. It is very likely that Barker happened to apply the stimuli to such points of the heart surface as did not lead to responses open to controversy and which definitely evoked extrasystoles of the corresponding type.

The method of eliciting ventricular extrasystoles through endocardial stimulation supplies further evidence against the usually accepted interpretation of the levo- and dextrocardiogram.

The results obtained are in complete agreement with the experimental and clinical evidence recently advanced in the literature.

#### REFERENCES

1. Barker, P. S., MacLeod, A. G., and Alexander, J.: The Excitatory Process Observed in the Human Heart, *AM. HEART J.* 5: 720, 1930.
2. Fahr, G.: Analysis of the Spread of Excitation in the Human Ventricle, *Arch. Int. Med.* 25: 146, 1920.
3. Oppenheimer, B. S., and Oppenheimer, E. T.: *Tr. A. Am. Physicians* 45: 427, 1930.
4. Lewis, T.: *Mechanism and Graphic Registration of the Heart Beat*, London, 1925, Shaw and Sons, Ltd.
5. Roberts, G. H., Crawford, H. J., Abramson, D. I., and Cardwell, J. C.: Experimental Bundle-Branch Block in the Cat, *AM. HEART J.* 7: 505, 1932.
6. Rothberger, C. J., and Winterberg, H.: Zur Kenntnis des Elektrogrammes der ventrikulären Extrasystolen, *Zentralbl. f. Physiol.* 24: 959, 1910.
7. Rothberger, C. J., and Winterberg, H.: Studien über die Bestimmung des Ausgangspunktes ventrikulärer Extrasystolen mit Hilfe des Elektrokardiogrammes, *Arch. f. d. ges. Physiol.* 154: 571, 1913.
8. Wiggers, C. J.: Muscular Reactions of the Mammalian Ventricle to Artificial Surface Stimuli, *Am. J. Physiol.* 73: 346, 1925.
9. Wilson, F. N., MacLeod, A. G., and Alexander, J.: The Excitatory Process Observed in the Human Heart, *AM. HEART J.* 5: 720, 1930.

# A STUDY OF THE ESOPHAGEAL LEAD IN CLINICAL ELECTROCARDIOGRAPHY\*†

## PART II. AN ELECTROCARDIOGRAPHIC STUDY OF AURICULAR DISORDERS IN THE HUMAN SUBJECT BY MEANS OF THE ESOPHAGEAL LEAD

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IN A recent communication<sup>3</sup> the theoretical and practical considerations pertaining to the use of the esophageal lead in clinical electrocardiography were subjected to critical assessment and the results of applying this method to 15 normal subjects and 35 patients with cardiac disease were noticed and discussed. A study has now been made of 92 additional clinical cases exhibiting abnormalities in the function of the auricles.

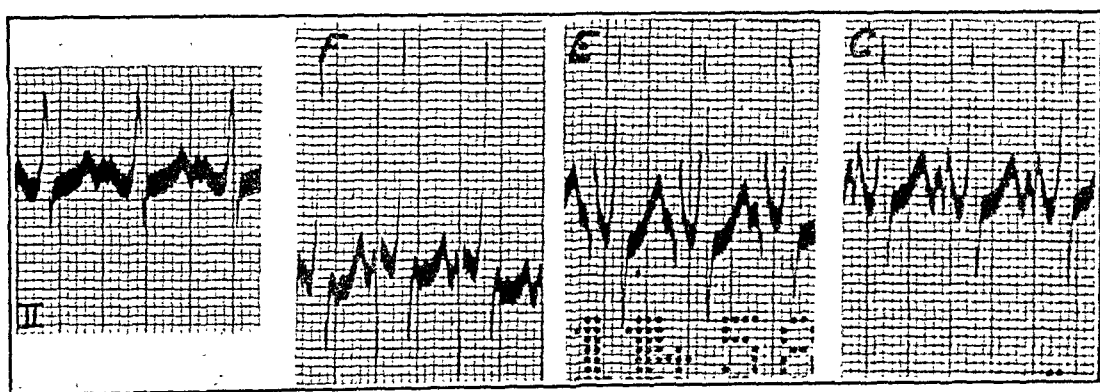


Fig. 1.§—Patient P. S. A case of simple auricular tachycardia. Lead II as designated. Curves F, E and C are esophageal electrograms from the regions indicated in Fig. 4A, part I.<sup>3</sup> Subsequently at a normal rate of heart action the esophageal lead yielded precisely similar complexes from these respective regions.

Owing to the diversity of conditions investigated in the present report, the subject matter has been divided into two parts: Section I is a miscellany comprising a variety of conditions—auricular tachycardia, mitral stenosis, hypertensive heart disease, myxedema and examples of hidden P-waves; Section II treats of auricular flutter and auricular fibrillation.

### SECTION I

*Auricular Tachycardia.*—Four cases of auricular tachycardia were studied. Two were examples of simple sinus tachycardia, and two were paroxysmal in nature. The former (Fig. 1.) showed P-waves which were in all respects, apart from their rate, similar to the P-waves of

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§Time: 0.01 sec. in all illustrations excepting those including two or three strings when it is 0.2 sec. Standardization: 1 mv. = 10 mm. unless otherwise specified.

the esophageal curves obtained in the same patients at normal rates of beating. The paroxysmal curves, on the other hand, were remarkable and merit further discussion.

The first example, taken from a man thirty years old who suffered from severe hyperthyroidism (B. M. R. +68), is illustrated in Fig. 2. Esophageal electrograms are shown from two auricular sites during the tachycardia and from the same points after the reversion to normal rhythm which followed thyroidectomy. The similarity of the form of

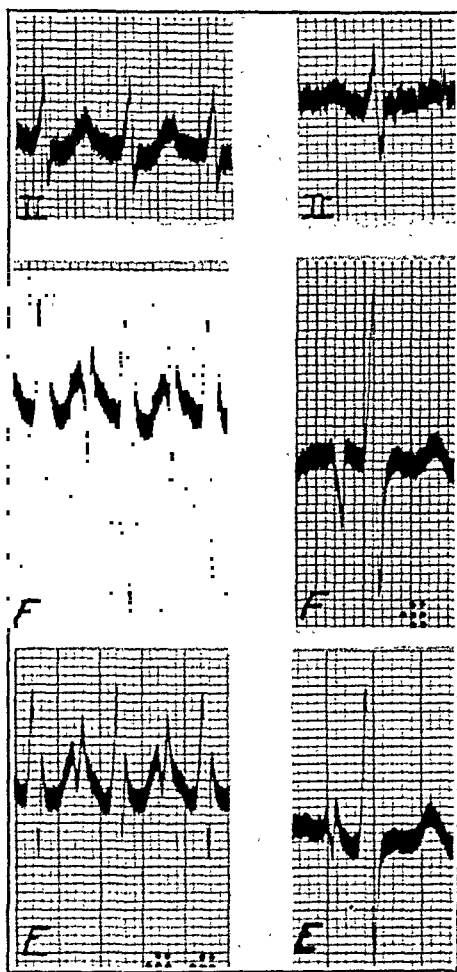


Fig. 2.—Patient H. D. Records from a case of paroxysmal auricular tachycardia taken during an attack and upon recovery. Lead II as designated. The esophageal records were obtained from the same auricular sites, respectively, at the two rates of beating. The letters on the esophageal curves refer to the regions marked in Fig. 4A, Part I.<sup>2</sup> A 2-to-1 heart-block is present. (See text for discussion.)

the P-waves at the two rates of beating, as taken from the same auricular areas, is strong evidence against an ectopic focus as the source of the tachycardia. If the responsible focus is ectopic it must lie extremely near to or, possibly, actually in the sino-auricular node.

There is an added and very important feature. The ventricle is responding to alternate beats of the auricle. The fact that a 2-to-1 A-V block is present is revealed on careful examination of the ventricular

complexes before and after recovery. In the normal or postoperative esophageal curves the upstroke of the S-wave merges smoothly into the beginning of the S-T segment, whereas in the curves showing tachycardia, there is an upwardly directed spike at the end of the S-wave. It is apparent also in one esophageal record that the hidden P-wave responsible for this abnormality varies slightly in its time of occurrence and alters the distribution of voltage in the QRS complexes by adding now to the R-wave and now to the S-wave. The rate of the auricle in this example must therefore be taken as being between 286

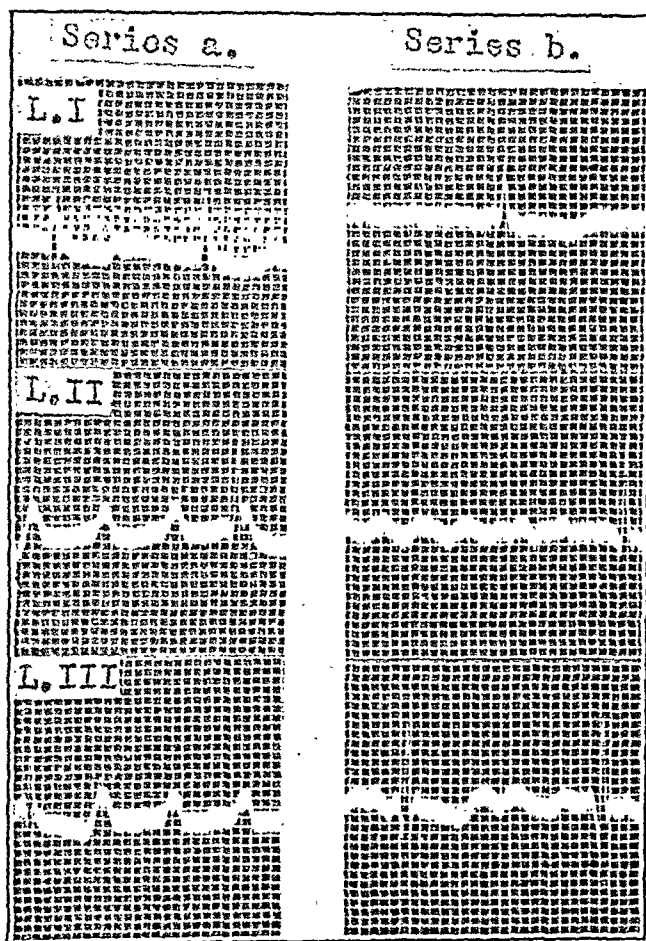


Fig. 3.—Patient S. F. Conventional Leads I, II, and III from a case of paroxysmal auricular tachycardia. Records of *Series a* were obtained during heavy digitalis administration; *Series b*, during a period of transitory auricular fibrillation before reversion to normal rhythm. (See text for full description of the case.)

and 300 beats per minute, a fact that was not suspected until after recovery, when the second esophageal examination revealed the true state of affairs.

The second case of paroxysmal tachycardia is of exceptional interest. Because it is believed to illustrate a very unusual clinical condition, it is deemed expedient briefly to describe the clinical history and findings.

The patient was a well-nourished, excitable, Jewish woman, aged forty years, who gave a vague history of rheumatic pains in childhood. From the age of seven, at which time she was told she had "heart trouble," she was subject to

exertional dyspnea. When she was thirty-two years old, she began to experience attacks of palpitation. The attacks began with lightning swiftness and subsided as quickly. At first these were of short duration but in January, 1935, the disorder became persistent. She had noticed that the attacks could often be terminated by holding her breath. At times there was severe substernal pain radiating to both arms, to the left shoulder blade, and to the neck. Swelling of the ankles, production of frothy blood-tinged sputum, and a terrifying feeling of weakness accompanied these episodes. She was admitted to the Sinai Hospital in Baltimore on Jan. 5, 1935, and a tentative, though disputed, diagnosis of auricular flutter was made. Auricular fibrillation was induced by the administration of a total of two grams of digitalis over a period of seven days. The fibrillation persisted for two days, after which spontaneous reversion to normal rhythm occurred. Figure 3 shows conventional records during the period of heavy digitalization and the period of auricular fibrillation.\* The patient was discharged on Feb. 14, 1935, without continuance of digitalis therapy. Three weeks later (March 8, 1935) she was admitted to the Johns Hopkins Hospital in considerable distress and severe pain of the type described above. On examination the ventricular rate was counted at 107 per minute. Venous pulsations of the veins of the neck were readily discernible at about twice this rate. On four occasions in as many days the patient was prostrated for long periods with severe pain, great apprehension, dizziness, orthopnea, extreme cyanosis, accompanied by frothy, blood-flecked sputum. During these periods the radial pulse became over 200 to the minute and the venous pulsations uncountably rapid. Vagal pressure was responsible for an occasional dropping out of auricular complexes at this rate (1a in Fig. 4), but at the usually prevailing rate only a slight decrease in the rate of the ventricle was observed. Electrocardiographic tracings at the slow rate showed a 2-to-1 block, with an auricular rate of 214 and ventricular rate of 107 per minute. During the more severe paroxysms the tracings showed an exact doubling of both these rates. Digitalis therapy was instituted and continued despite the appearance of severe toxic symptoms until, when 2.1 gm. had been given in seven days, the rhythm reverted to normal. She was discharged on April 13, 1935, after a carefully graduated course of physical therapy and exercise, on a maintenance dose of digitalis. This was efficacious in preventing a reappearance of the arrhythmia for a period of five months.

The clinical diagnosis presented a problem of considerable difficulty owing to the presence of harsh systolic and diastolic murmurs at the pulmonary area and softer but independent double murmurs at the apex. There was considerable enlargement of both auricles and of the pulmonary conus. The possibility of pulmonary and mitral stenosis in the presence of a patent interauricular septum was entertained. The paroxysms were generally accepted by various clinicians as being due to auricular flutter.

The records of this case are shown in Fig. 4. Curves 1a and 1b show the conventional Leads II and III, respectively, at the fast rate (auricles 428 per minute). Of interest are the occasional instances of auricular block occurring during vagal pressure. This feature in association with the very fast rate at once throws suspicion on a diagnosis of auricular flutter. Curves 2a, 2b, and 2c show the conventional Leads I, II and III and curves 2d, 2e, and 2f, the esophageal electrograms at the usually prevailing rate of 214 auricular contractions per minute. Curves

\*The writer is greatly indebted to Dr. Austrian and Dr. Katzenstein for their courtesy in permitting examination of the patient at the Sinai Hospital, for the permission to publish the records in Fig. 2, and for the opportunity of further study of the patient at the Johns Hopkins Hospital.

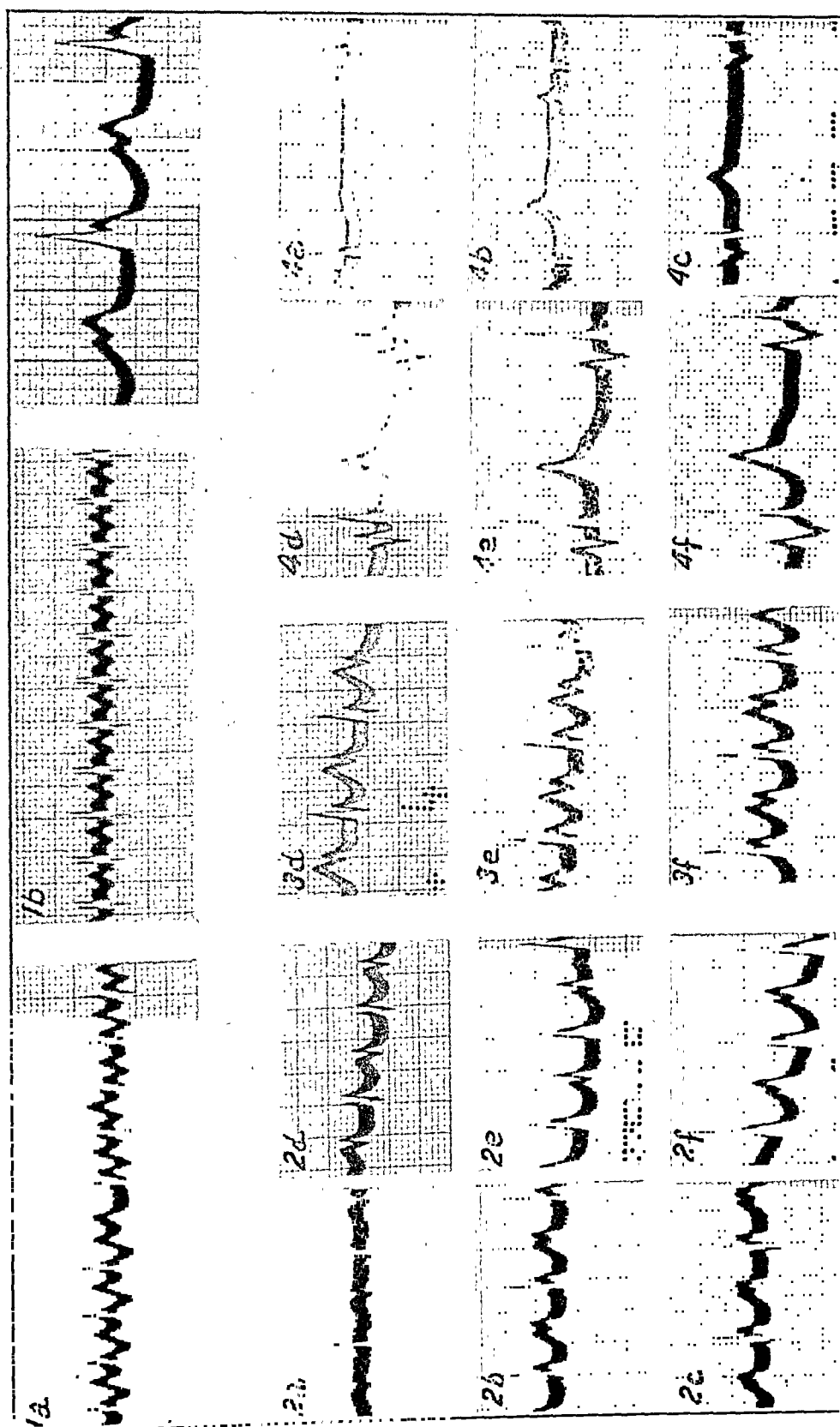
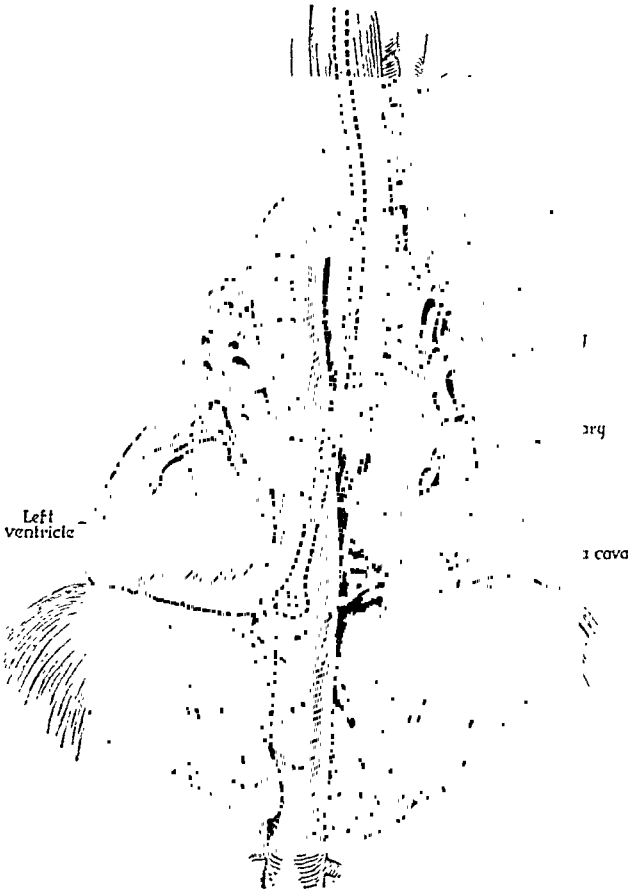


Fig. 4.—Patient S. F. Paroxysmal auricular tachycardia showing conventional and esophageal records. The figure is fully described in the text.

3*d*, 3*e*, and 3*f*, taken at the same rate, are esophageal electrograms taken near the height of digitalization while 4*d*, 4*e*, 4*f*, and 4*a*, 4*b*, 4*c*, respectively, are esophageal and conventional Leads I, II and III after recovery of normal rhythm. All electrograms here compared are from corresponding auricular sites. Series "d" are from the lower part (corresponding to region G in Fig. 4 A, Part I<sup>3</sup>). Series "e" are from a point 2 cm. above "d," and series "f," 2 cm. above "e." The unmarked esophageal curve photographed at double camera speed is taken at the habitual or persistent cardiac rate (auricles 214 per minute).



\*Fig. 4A.—Drawing of a posterior surface of the human heart to illustrate the position of the esophagus in relation to the left auricle and the left ventricle. The lettered areas indicate the regions tapped by the electrode.

The conventional records have twice been erroneously diagnosed as auricular flutter. Certainly the combination of definite, if deformed, P-waves in the esophageal curves in the presence of an unmistakable return to the isoelectric line is proof that at the usually prevailing rate, 214 auricular and 107 ventricular contractions per minute, a 2-to-1 block of an auricular tachycardia was present. When the records of this and the preceding patient are compared with the examples of true flutter

<sup>3</sup>Reprinted from Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography, Part I. AM. HEART J. 12: 1, 1936.

(Section 2), there can be no doubt that the mechanisms underlying the two conditions are quite dissimilar. This point receives additional stress in the later discussion of auricular flutter, but for the present these two cases are offered as evidence that 2-to-1 A-V block does occur in paroxysmal auricular tachycardia and that the auricular rate in this condition may rise, certainly to 300, and very probably as high as 428 beats per minute. The regrettable lack of esophageal electrograms at the faster rate makes certainty impossible, but the probability that the mechanism responsible is still that of paroxysmal tachycardia and not flutter is strengthened by the curious dropping out of auricular complexes seen in conventional Lead II (1a in Fig. 4) on vagal pressure. There also seems to be little doubt that the focus from which the abnormal rhythm arose is different from that responsible after normal rhythm was reestablished, but there is such gross deformity of the P-waves in both esophageal and conventional curves under conditions of normal rhythm that the matter cannot be settled with finality.

The markedly abnormal character of P-waves of the esophageal electrograms in this case is the subject of reference later in this report. A most remarkable feature in this connection is that, although the patient was examined on ten separate occasions, the only area of auricular muscle to yield defined intrinsic deflections in the auricular complex was the lower pole of the left auricle. If the electrode was raised 2 cm. above this area, despite the fact that the auricles were larger than normal, the P-complexes lost all trace of a sharply defined intrinsic deflection. The degree of P-wave deformity is best appreciated by comparing the curves under consideration with the normal curves of Fig. 4 B, Part I,<sup>3</sup> but the underlying cause of the deformity remains unknown.

*Mitral Stenosis.*—Samojloff and Steshinsky<sup>31</sup> long ago pointed out in cases of mitral stenosis that the character of the P-waves in conventional leads changes with the clinical condition. In a patient who had high P-waves, they observed that, as congestive failure developed, the P-waves became of progressively lower amplitude.

The first point of interest in the present study of twenty-four cases of suspected mitral stenosis with normal rhythm is to determine whether the height of the intrinsic deflection in the esophageal electrogram is greater when the amplitude of the P-wave of Lead II is increased. Figure 5 provides an answer to this query and is an example of a relationship found in nearly all cases uncomplicated by congestive failure. In general, a high or low P-wave in conventional Lead II yields respectively great or small amplitude of intrinsic deflections in the electrograms.

The twenty-four cases were divided into four groups: A, patients who had had rheumatic fever but who had neither a diastolic mitral murmur nor discernible enlargement of the left auricle; B, patients



who had diastolic mitral murmurs and slight enlargement of the left auricles; C, patients who had diastolic mitral murmurs, large left auricles but no sign of congestive failure; D, patients with mitral stenosis and in congestive failure. A study was made of the esophageal records in each of these cases. In every instance at least six such records were taken from the various auricular sites, and those which showed greatest amplitude in the P-waves were chosen for comparison with the normal control series.

Those cases which fell into Group A showed electrograms which could not be distinguished from the normal controls. Those in Groups B and C showed increased height of the intrinsic deflections as in Fig. 5. The cases in Group D all showed some, and often a very marked, diminution of the amplitude of the intrinsic deflections (Fig. 6).

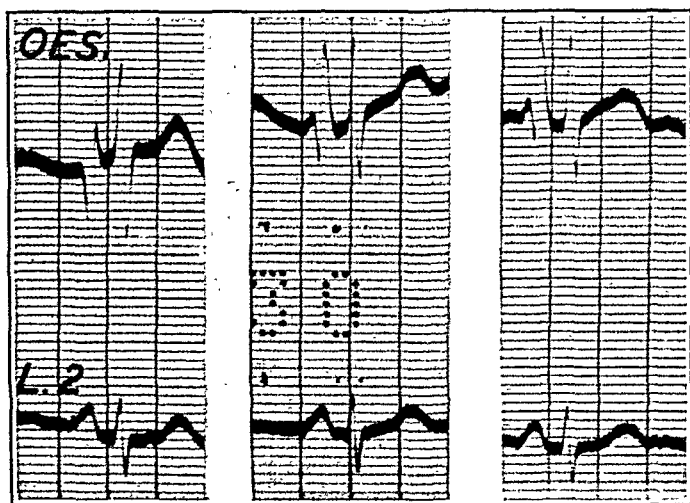


Fig. 5.—Patient H. M., with mitral stenosis. Simultaneous records from the esophageal lead and conventional Lead II to illustrate that high voltage P-waves in conventional leads are represented by an increased amplitude in the intrinsic deflection of esophageal electrograms.

In addition to these findings, another abnormality of the P-waves of the electrograms was frequently seen. This was a deformity or slurring of the extrinsic waves (see Fig. 4 B, Part I<sup>3</sup> for comparison). It occurred most frequently in Group D. The curves shown in Fig. 7 were obtained from a man who had on four separate occasions been admitted for congestive failure, with normal rhythm. He was the only patient in this series of cases of mitral stenosis who developed auricular fibrillation and in whom a comparison could be made of the electrograms in both rhythms. Of like importance was the case of mitral stenosis considered in the section on auricular tachycardia (Fig. 4). In the records obtained after normal rhythm was reestablished there was only one auricular site which yielded electrograms showing no serious deformity of the P-wave. In the other two esophageal curves which were obtained when the electrode was contiguous to the middle

and upper portions of the dilated left auricle, striking deformities of the wave were present.

On the slender evidence which these few cases provided, it is manifestly impossible to arrive at definite conclusions. It is, nevertheless, fair to suggest that these gross deformities of the P-wave of the electrogram indicate interference with the even spread of the excitation wave. No post-mortem evidence is as yet available to aid in the interpretation of what these changes mean in terms of the underlying pathology of the auricle. It can only be said that deformities of this character preceded by four months the onset of auricular fibrillation

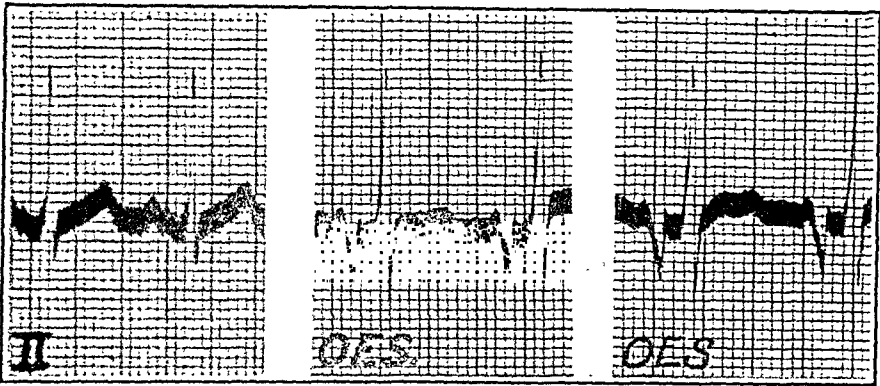


Fig. 6.—Patient L. F. From a case of mitral stenosis. Lead II and two examples of esophageal leads. The latter show decreased amplitude of the intrinsic deflection with slurring of the extrinsic portions of the complex.

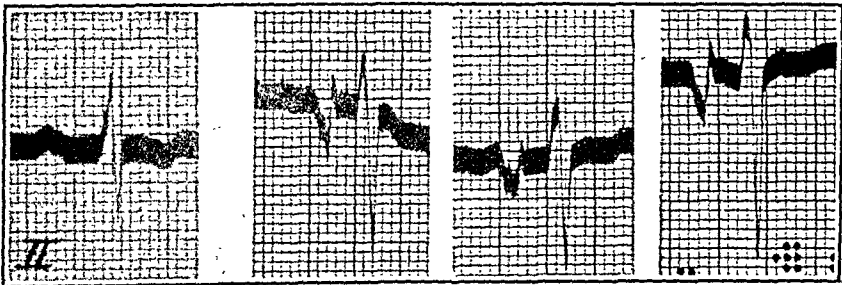


Fig. 7.—Patient T. G. Lead II and three esophageal leads from a case of mitral stenosis in congestive failure. The esophageal curves show marked slurring of the extrinsic parts of the complex. (See text.)

in one case and that they both preceded and followed attacks of very rapid tachycardia (up to 428 per minute) in the other. The facts do, however, give grounds for the belief that a wider use of the esophageal lead in cases of mitral stenosis would soon yield evidence of considerable prognostic value.

*Hypertension.*—Increased amplitude of the P-waves of conventional leads is most commonly found in pulmonary and mitral stenosis and in hypertension.<sup>1, 25, 34</sup>

Esophageal leads have been taken in twenty-eight cases of hypertension. It may be said that the same general relationship between the height of the intrinsic deflection of the esophageal electrograms and the

amplitude of the P-wave in Lead II holds here as in mitral stenosis. The appearance of congestive failure has also much the same effect in diminishing the amplitude of the intrinsic deflections.

There are, however, certain differences between the auricular electrograms in the two diseases. In severe hypertension the intrinsic deflections start far below the isoelectric line and seldom rise much above it (Fig. 8), whereas in mitral stenosis the greater part of the intrinsic deflection usually lies above the isoelectric line. The initial belief that both the distinctive character and the increased amplitude were dependent upon the actual degree of hypertension (blood pressure levels) has been proved to be unsound. The entire series of 142 cases was then reexamined to discover the clinical associations of the occurrence of P-waves of this particular type. Eighty per cent (22 cases) of those which showed such P-waves had diastolic pressures of over 110 mm.; the remainder had diastolic pressures ranging from 107 to 55 and included two cases of severe aortic insufficiency. On the other hand,

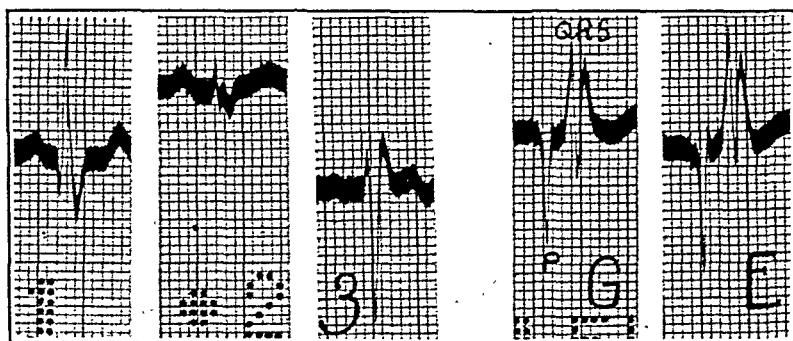


Fig. 8.—Patient E. C. From a case of severe hypertension showing the characteristic type of P-wave in the esophageal electrograms in this condition. There is also a splitting of the QRS complex which is probably indicative of intraventricular delay. The letters G and E indicate the levels of the esophageal electrode in terms of Fig. 4A, Part I.<sup>2</sup>

some cases of early, though severe, hypertension did not exhibit the type of P-wave under discussion.

After further investigation it has been found that the downwardly projected P-waves of the electrogram occur in the presence of great enlargement of the left ventricle. With the discovery of this common denominator the temptation is strong to suggest the following explanation of the findings: If, in the absence of enlargement of the left auricle, the left ventricle is enlarged sufficiently to displace the heart backward and, by its impingement on the chest wall, to the right; then the total effect is a relative “displacement” of the esophagus to the left. This change in turn causes an increase in the amount of auricular musculature lying between the esophageal electrode and the sino-auricular node. The net result is, therefore, a displacement of the intrinsic deflection, for any given esophageal site of the electrode, to a position relatively later in the P-wave than would normally be the case.

The wave "c" (Fig. 5, Part I<sup>3</sup>) is therefore prolonged and the wave *i* starts and finishes, respectively, lower and later than usual.

The experimental basis for the above theory is implied in the work of Lewis, Meakins, and White.<sup>18</sup> Further confirmation is presented in Fig. 9, taken from an experiment on a dog weighing 11 kg. The operative and galvanometric details are similar to those described in Part I, Fig. 2.<sup>3</sup> The leads are also similar except that in this experiment two direct leads (by wool extensions from nonpolarizable kaolin-saline copper-sulphate electrodes) were fixed to the right auricle, and each galvanometric circuit was completed through indifferent electrodes on the left

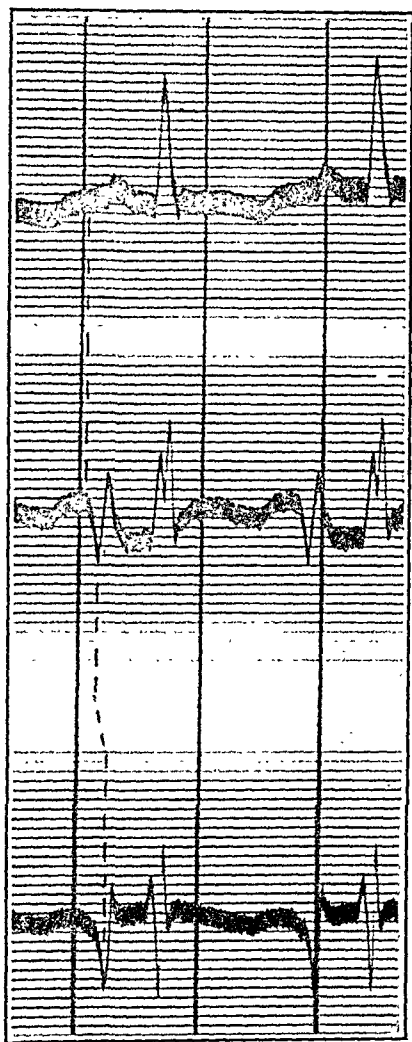


Fig. 9.—Conventional Lead II and two direct leads from the surface of a dog's right auricle, taken simultaneously. Fifteen millimeters of auricular muscle separated the electrodes from which the middle and the lower records were obtained. The delay in the onset of the intrinsic deflection is indicated by the lower dotted line. (For further details see text.)

hind leg. The lower curve is taken from an electrode placed near the base of the right auricular appendix and the middle curve from an electrode 15 mm. nearer the tip of the appendix. Upward deflections in the records indicate electronegativity of the direct electrodes. Lead II is shown above.

The intrinsic deflection of the direct lead taken farthest from the sino-auricular node occurs 0.0184 sec. later than the intrinsic deflection from the body of the auricle and begins far below the isoelectric line. The differences in time of occurrence and in form of these two intrinsic

deflections are attributable solely to the fact that excitation at the distal electrode occurred later than at the proximal. This in turn is due to the fact that the proximal electrode was about 15 mm. closer to the sino-auricular node than was the distal electrode.

This hypothesis was also put to a simple clinical test in five normal subjects. The esophageal electrode was passed to a depth at which it lay in a position corresponding to region F (see Part I, Fig. 4 A<sup>2</sup>). Records were then taken with the subject lying first on the back and then on the right side. Comparisons of the records in each instance consistently showed a slightly later and lower onset of the intrinsic deflections when the subject was in the lateral posture than was seen in those records obtained in the supine position. The intrinsic deflections also did not rise as high above the isoelectric line when the patient was lying on the side. These findings were attributed to a shift of the heart to the right, resulting in a relative though slight displacement of the esophagus to the left.

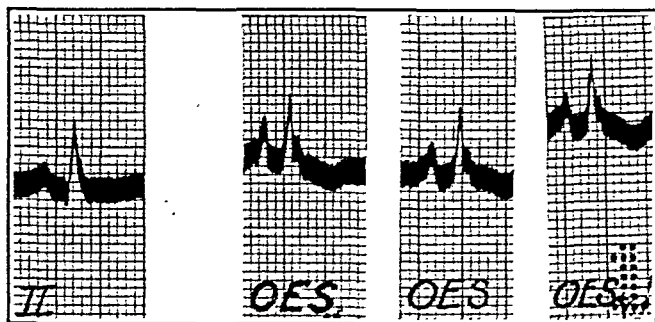


Fig. 10.—Patient O. G. Conventional Lead II and three esophageal curves. Case of myxedema. B.M.R. = -30. Note that there are no intrinsic waves in the esophageal electrograms and that the voltage remains low in these records. All curves standardized 1 mv. = 10 mm.

*Myxedema and Hyperthyroidism.*—Only four cases of myxedema and five of hyperthyroidism are included in the present series. It is not proposed in this report to discuss at length the findings in hyperthyroidism apart from those instances in which the condition is associated with particular arrhythmias. The P-waves of the hyperthyroid patients with normal rhythm show an apparently normal contour, with an amplitude of the intrinsic waves within the upper range of normal findings. Certain peculiarities of detail may be reported at a later date, but the findings have not yet been subjected to full experimental proof.

Zondek,<sup>36</sup> in his original paper, pointed out that low or absent P-waves were a characteristic of the myxedematous heart. After the controversy over the cause of the low voltage in electrocardiographic curves in myxedema (Leug,<sup>10</sup> Means, White, and Kranz<sup>22</sup>), this finding was relegated to obscurity from which it has been recently revived by Tung<sup>33</sup> and Hallock.<sup>8</sup>

In the myxedema cases of this series there was a remarkable distortion of intrinsic deflections of the P-waves in esophageal electrograms.

In one instance this appeared in the absence of either clinical or radiological evidence of enlargement of the heart. In the only case (Fig. 10) which showed low voltage in conventional leads, and in which great enlargement of the heart was present, not only were the P-waves greatly deformed but there was no increase in the voltage of the ventricular curve in the esophageal records.

Although the number of cases investigated is very small, the results suggest that not only is the low voltage of myxedematous hearts to be explained on a basis of an inherent defect in the myocardium and not to increased skin resistance, but also that one of the earliest signs of "myxedema heart" is to be found in decreased voltage and slurring of the intrinsic deflection of the auricular complex in esophageal leads.

*The Use of the Esophageal Lead in the Discovery of Hidden P-Waves.*  
—In the experience of everyone who has studied large numbers of

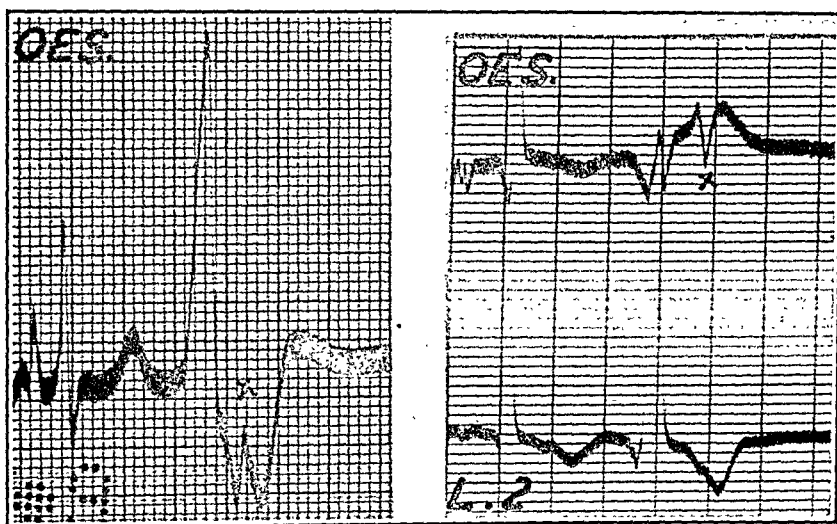


Fig. 11.—Patients S. A. and P. S. Two examples of retrograde P-waves shown hidden in the T-waves of ventricular extrasystoles are indicated by crosses. In the double record the esophageal lead shown above has been obtained with the electrode below the level of the left auricle. In the single string record the esophageal electrode lies near the upper pole of the left auricle.

electrocardiographic tracings, there occur instances when it is virtually impossible to be certain of the position and presence of the P-wave. In the present series a few interesting examples of this have been encountered. Mention has already been made of one case of auricular tachycardia in which the use of the esophageal lead supplied evidence of a decisive character (Fig. 2). Two additional examples merit illustration.

In Fig. 11 are shown two examples of hidden P-waves occurring as the result of retrograde excitation of the auricle in cases of ventricular extrasystoles. The character of these P-waves clearly denotes their ectopic origin. A curious feature of retrograde P-waves as seen in the esophageal curves is also illustrated, namely, the remarkable amplitude and definition of the waves, when compared with those of sinus origin. It has already been shown (Fig. 4 B, Part I<sup>3</sup>) that, when the esophageal

electrode is situated below the level of the lower pole of the left auricle, the P-waves lose their intrinsic deflections and become poorly defined. It is to be anticipated that retrograde P-waves would undergo similar

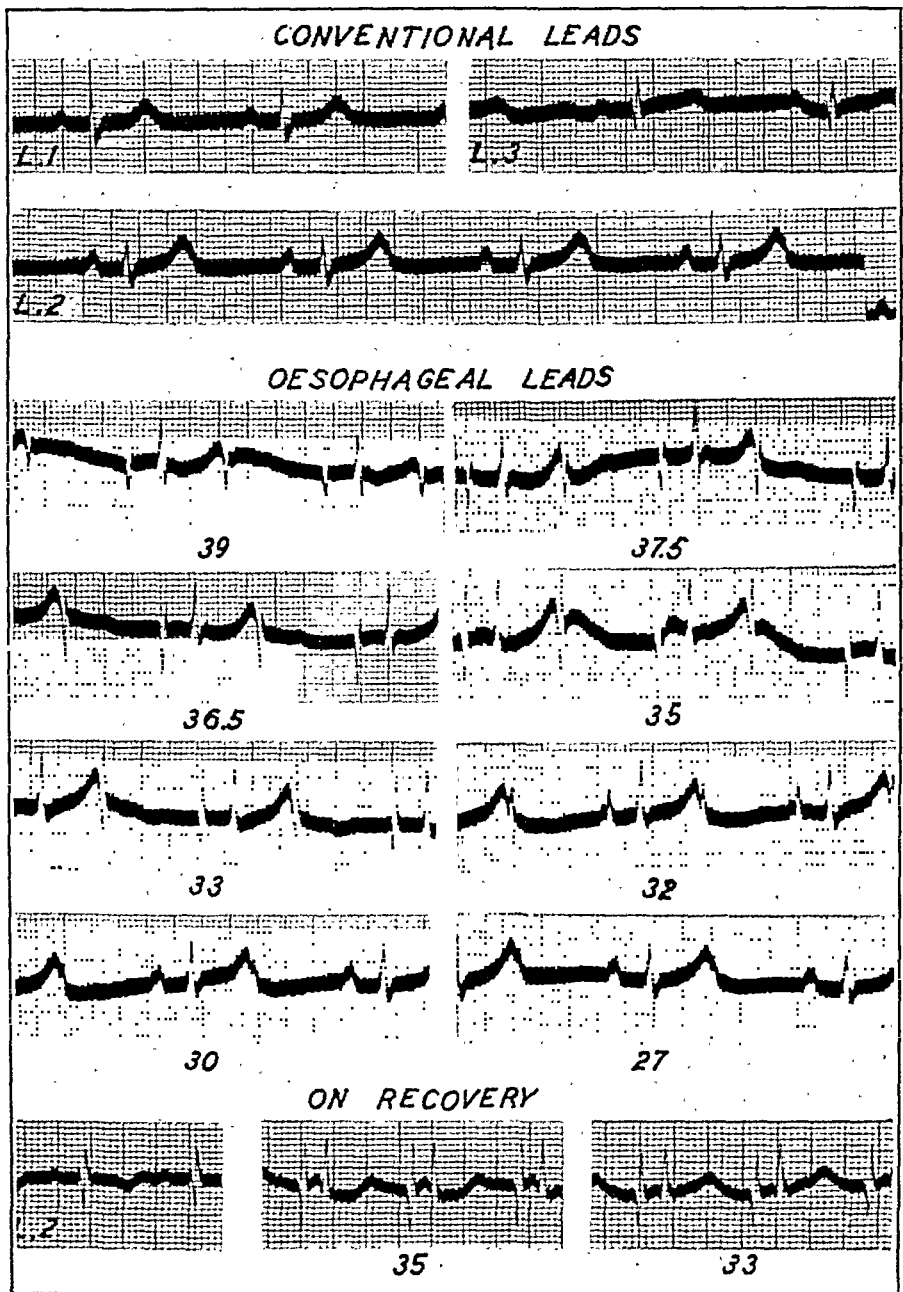


Fig. 12.—Patient E. L. Conventional and esophageal leads taken from the same patient at two different rhythms. Conventional leads during 2-to-1 block are indicated above. The segregated eight records in the central part of the figure are esophageal leads obtained with the electrode at the depth in centimeters indicated below each record. The lower line shows Lead II and two esophageal electrograms on recovery of normal rhythm.

changes. This appears, however, not to be the case, for this type of wave as well as certain other types of ectopic P-waves remains sharply defined in electrograms obtained from the ventricle. It is difficult to

provide a convincing explanation of this fact though the possible early excitation of the sleeve of musculature on the inferior vena cava may be the cause.

Another, though not quite perfect, example of hidden P-waves is shown in Fig. 12. The practice of showing only sample curves, which has, in the interest of space, been followed in other examples, is here departed from, and esophageal curves from all levels of the electrode are included. This serves not only as a demonstration of the way in which the method has been applied to the subjects of the series as a whole, but is instructive in showing the abrupt change in the character of the P-wave once the electrode has lost its proximity to the auricle.

From a cursory examination of the conventional curves the diagnosis is extremely likely to be one of first degree heart-block, but closer scrutiny leads to the detection of abnormalities in the form of the T-waves of Lead II. The esophageal curves give a clear explanation of this small discrepancy and establish the diagnosis of 2-to-1 heart-block beyond all doubt. After the upper limit of the auricle has been passed (between positions 33 cm. and 32 cm.), there is a rapid return of the P-wave to obscurity, and in the last position (27 cm.), where the electrode is lying near the arch of the aorta, the curve is very like that of conventional Lead II.

### *Recapitulation of Section I*

The value of the esophageal lead lies in its exploratory principle. Its application in this capacity to the left auricle produces electrograms of a perfectly definite nature: the P-waves having an increased amplitude, a polyphasic form, and showing an intrinsic deflection. In a comparative study of the form of the waves under conditions of disease, decisive evidence has been forthcoming in regard to the distinctive character of auricular tachycardia as contrasted with auricular flutter. So far as functional disturbances of the auricle are reflected in electromotive changes, the esophageal lead is of great value in detecting the latter. In a limited number of cases of mitral stenosis and of myxedema the findings have strongly suggested that a wider use of the method might soon produce information of diagnostic and prognostic importance. The use of the method for the discovery of hidden P-waves has been demonstrated.

### *Summary of Section I*

The esophageal lead has been employed in a study of certain abnormalities of the auricular complexes and of the rhythmic function of the auricles in sixty-seven human subjects.

Esophageal (auricular) electrograms from patients illustrating the following conditions have been reproduced and discussed.



Auricular tachycardia; simple sino-auricular and paroxysmal types (the latter showing 2-to-1 heart-block).

Mitral stenosis of varying grades of severity.

Hypertensive heart disease.

Myxedema and hyperthyroidism.

Hidden P-waves in heart-block and retrograde excitation from ventricular sources.

## SECTION II

### *The Esophageal Lead in Clinical Cases of Auricular Flutter and Auricular Fibrillation*

From an electrocardiographic point of view the outstanding contribution of the esophageal lead is the demonstration of the intrinsic deflection of cardiac action currents in the living human subject.<sup>3</sup> This characteristic of esophageal electrograms has been recognized by Lieber-son and Liberson,<sup>19</sup> who were the first to publish a clinical record obtained by the lead. The importance of the finding lies in the fact that the method thus spans the gap between clinical electrocardiography and the results of animal experimentation. The hypotheses advanced to explain the various cardiac disorders as detected by indirect clinical leads are almost without exception based upon experiments on the exposed hearts of various other mammals. The transference of such results to the human subject has, in general, stood the test of time, but it has always, and legitimately, been open to a certain measure of doubt. This has been notably the case in regard to auricular flutter, auricular fibrillation, and the allied arrhythmias; for such disorders are usually the expression of disease, often of long standing, in the human subject. Conditions very like, if not identical to, them may be reproduced in healthy experimental animals by an appropriate technic. The question arises whether the experimental findings and theories based upon such findings are wholly applicable to the human subject.

Fibrillation has been observed occurring as the result of disease in horses<sup>12</sup> and dogs<sup>27</sup> on direct examination of the auricles of the exposed hearts. The gross appearances are very similar to auricular fibrillation as seen in the experimental animal. Fluoroscopic observations of the auricles in human subjects suffering from auricular flutter yield appearances indistinguishable from those seen in experimental animals. The strongest evidence brought in support of the thesis that the conditions occurring in man are identical to those produced in animals has, however, been obtained by the electrocardiograph. Lewis and his collaborators<sup>17</sup> have shown that a distinctive form is characteristic of auricular flutter waves obtained by leading directly from the auricular surface in dogs. They have shown that indirect leads obtained from such animals are indistinguishable in character from those occurring in conventional leads in human cases of auricular flutter. Moreover,

they have advanced<sup>13, 14, 15</sup> well-founded evidence in support of the theory that in both animals and man auricular flutter is due to a mechanism characterized by a single excitatory wave progressing with a "circus movement."

It is no part of the objective of the present report to attempt to prove or disprove accepted hypotheses. The facts which are offered are of interest because they supply one missing link in the above cited chain of evidence. The importance of such evidence as is offered is magnified by the fact that most observers believe auricular flutter, impure flutter, and auricular fibrillation are due to the operation of a common fundamental mechanism.<sup>11, 2</sup>

*Auricular Flutter.*—Four cases of auricular flutter were studied by the esophageal lead. They all differed with respect to etiology, and, as all recovered normal rhythm, a comparison was possible between curves obtained from the same auricular sites during and after the attack.

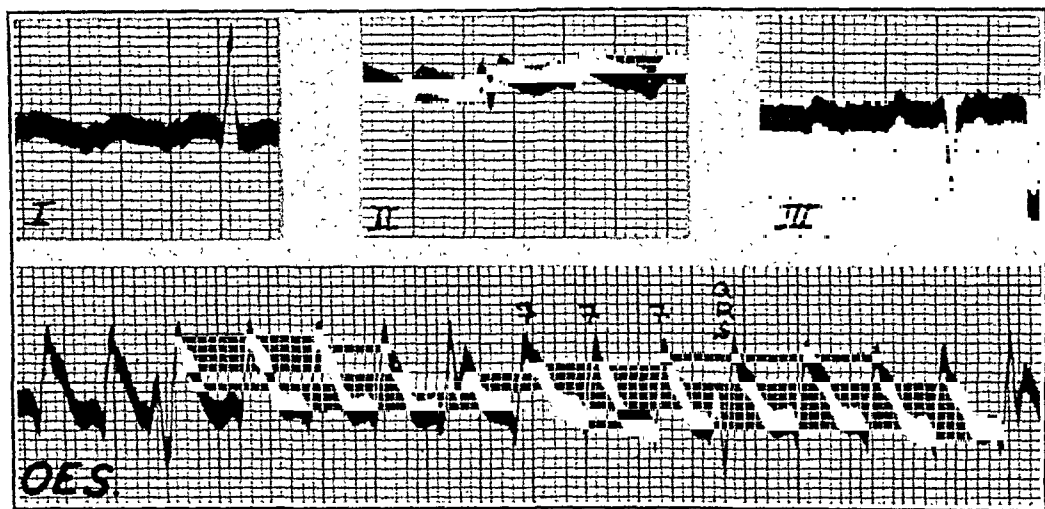


Fig. 13.—Patient W. E. Case of auricular flutter showing conventional Leads I, II, and III and an esophageal record. Flutter waves marked *F*. Standardization in each case 1 mv. = 10 mm.

The first patient was a busy executive aged fifty years who had neither history nor sign of rheumatic disease or of hyperthyroidism. He was severely arteriosclerotic but exhibited no hypertension. Flutter developed during a grave physical and mental breakdown apparently the result of overwork and strain.

In Fig. 13 conventional and esophageal curves are shown taken during the period of flutter. The character of the flutter waves is remarkably different from the normal type of P-wave and may with advantage be contrasted with those of simple auricular tachycardia (Fig. 1). The waves have a great amplitude, quite overshadowing, in some curves, the ventricular complexes. The stride of the waves is very long, one wave being terminated as the next begins.

After recovery on quinidine therapy the P-waves, where they occur (Fig. 14), show a prolongation of both the duration of the intrinsic

deflection and the whole P complex. Both these factors may be due to subnormal conductivity in the auricular tissue. Here and there the P-waves are completely absent, and the rare condition of sino-auricular standstill is seen, caused in all probability by the heavy dosage of quinidine (14.7 gm. over a period of nine days).

The second case was a thirty-year-old man who had a severe grade of hyperthyroidism (B. M. R. up to +88). Conventional and comparable esophageal curves before and after spontaneous recovery following thyroidectomy are shown in Fig. 15. The great difference between the character of flutter and normal P-waves is again illustrated in this case.

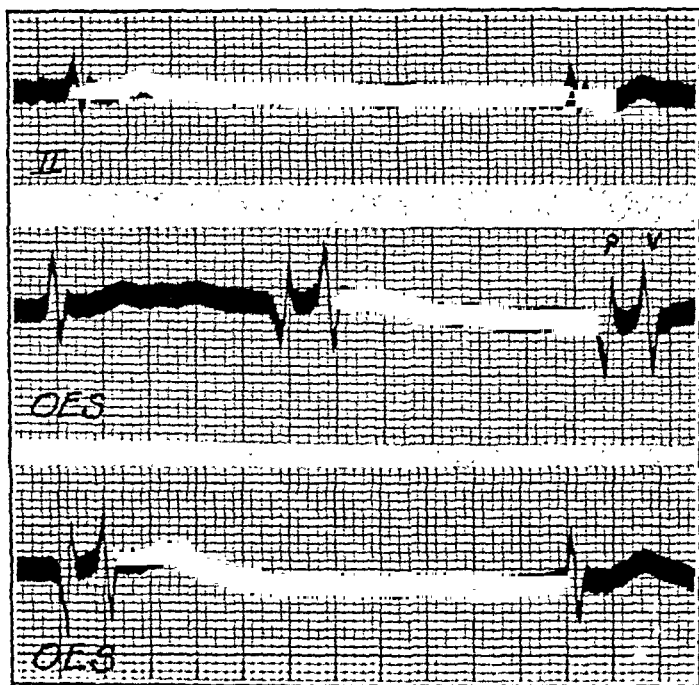


Fig. 14.—Patient W. E. Conventional Lead II and two esophageal records from the same subject as Fig. 13, after flutter had disappeared on quinidine therapy. The esophageal electrogram shows an example of auricular standstill with ventricular escape. The P-waves have a longer duration than normal. P-waves indicated by P, QRS complexes by V. Standardization 1 mv. = 10 mm.

These two examples leave no reasonable doubt that an abnormal and characteristic mechanism underlies auricular flutter. The esophageal electrograms of both show a close resemblance to the experimental curves of Lewis and his coworkers<sup>17</sup> from the dog\*. They afford a clear indication that flutter occurring in the human subject is similar to that produced artificially in dogs.

The third case of flutter was paroxysmal in nature. It occurred in a man fifty-five years old who had suffered from occasional prostrating attacks of tachycardia over a period of nine years. His history was

\*Lewis' curves were obtained by double direct electrodes on the auricle in contradistinction to those derived with the esophageal lead.

noncontributory from an etiological point of view. He showed no signs of arteriosclerosis, hyperthyroidism, or mitral stenosis. On numerous occasions electrocardiographic investigations had been made without an accurate diagnosis being attained. He had acquired an addiction to morphine derivatives as a sequel to the frequent therapeutic use of these drugs for his disability. The curves here presented were obtained during and after a brief attack which occurred at the Johns Hopkins Hospital while he was under treatment for drug addiction.

Figure 16 shows the conventional Lead II and esophageal leads taken simultaneously. Apart from the decisive evidence given by the esophageal lead in determining the correct diagnosis, there is an additional

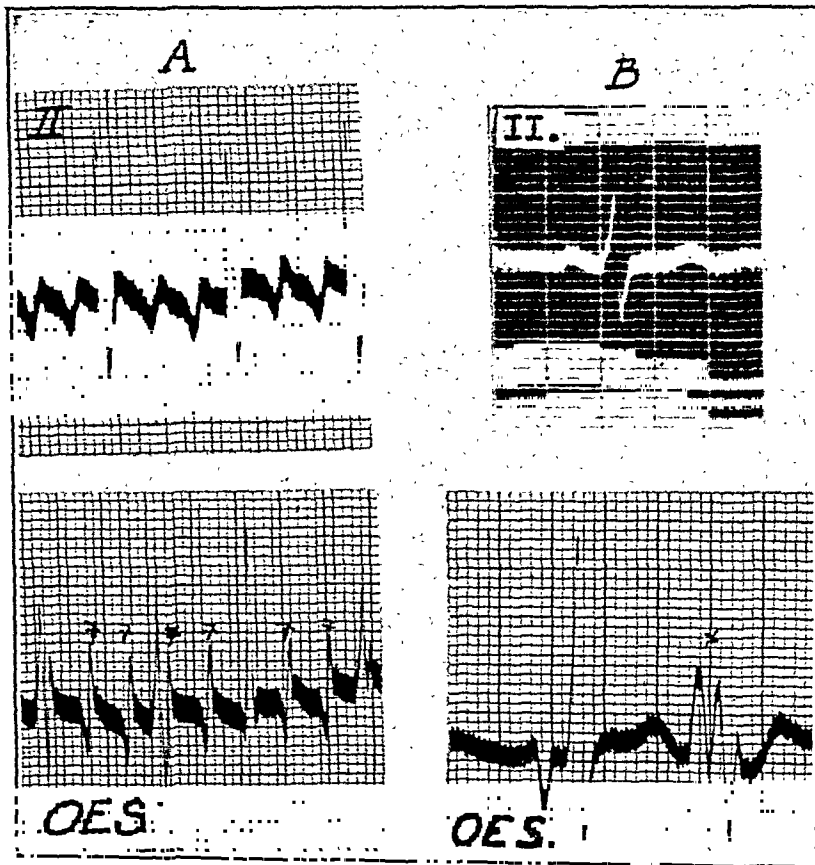


Fig. 15.—Patient W. D. Case of auricular flutter due to hyperthyroidism (Series A) and after recovery of normal rhythm (Series B). The conventional Leads II are indicated above, and esophageal electrograms taken from respectively the same auricular sites are shown below. Esophageal record taken during normal rhythm shows a ventricular extrasystole and slightly deformed P-waves. The patient showed signs of myxedema when the curves of Series B were obtained.

phageal lead in determining the correct diagnosis, there is an additional point of importance. Examinations of the curves show that the rhythm is a regular 2-to-1 flutter, the auricles beating at 300 and the ventricles at 150 per minute. A comparison of the time relationships between the intrinsic deflections in esophageal curves and the upstroke of the flutter waves in Lead II reveals progressive differences. As the electrode is moved downward to successively lower auricular sites, the intrinsic deflections in the electrograms become progressively earlier in occurrence

with respect to both the R-waves and the upstroke of the flutter waves in Lead II (as is indicated by the vertical dotted lines in Fig. 16). The actual times of occurrence of the intrinsic deflections are shown in Table

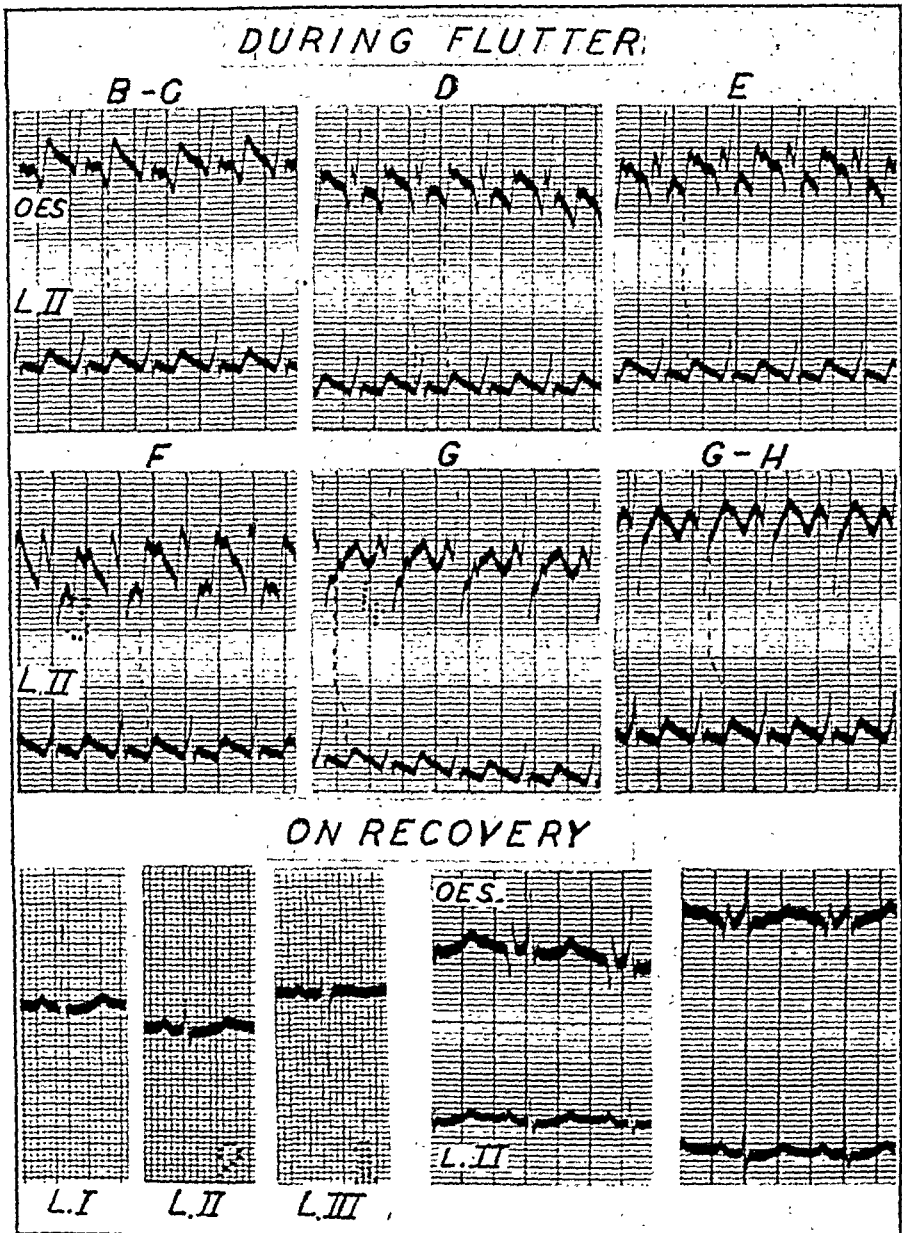


Fig. 16.—Patient D. R. From a case of paroxysmal auricular flutter during the attack and on recovery. Analysis of flutter waves is shown in Table I. The letters above the records in flutter indicate the position of the esophageal electrode in terms of Fig. 4A, Part I.<sup>3</sup> The dotted lines indicate the progressively changing relationships of the intrinsic deflections in the esophageal electrograms to the onset of flutter waves in conventional Lead II. Examples of conventional curves and of esophageal electrograms after recovery are shown below. (See text and Table I for discussion and data.)

I. It is apparent that in the region of the superior vena cava and the uppermost portion of the auricle the intrinsic deflections arise slightly later than the corresponding upstroke in Lead II. In the mideaval re-

gion, on the other hand, they are earlier by 0.0294 sec., while lower down, near the inferior vena cava, they occur 0.0734 sec. before the flutter wave of Lead II. This finding stands in contrast to the position of the intrinsic deflection in the P-complexes of normal curves (see Fig. 4 B., Part I<sup>3</sup>), where the earliest intrinsic deflections are obtained when the electrode is closest to the sino-auricular node. For positions of the electrode above and below this point (contrast curves C and E with D of Fig. 4 B, Part I<sup>3</sup>) the intrinsic deflections are always later with respect to the onset of the P-wave. The data of Table I quite definitely show that the flutter wave activated the inferior part of the left auricle about 0.06-0.08 sec. earlier than the upper part of the auricle. In other words, important evidence is here provided to augment that of Lewis<sup>13</sup> and his collaborators<sup>15</sup> to the effect that auricular flutter is due in man to a "circus movement." Under the conditions imposed by the esophageal method, only the left auricular segment of the circus pathway can be investigated. The findings here reported lose none of their significance if it is held that the areas tapped are not necessarily on the actual path of the "central" or "mother" wave, for the times of occurrence of the centrifugal waves are dependent upon the time of excitation of the contiguous central path.

In the section on paroxysmal auricular tachycardia (Section I) two unusually interesting cases of 2-to-1 block were discussed. The second of these cases (Fig. 4) on occasion exhibited an auricular rate of 428 per minute. Although esophageal electrograms were not obtained at the faster rate, the diagnosis of paroxysmal auricular tachycardia was entertained for reasons which were discussed at some length.

At this point it is expedient to point out why both of the cases cited cannot be considered to be due to auricular flutter. The curves from three undoubted cases of auricular flutter have been recorded above. The esophageal electrograms of these cases show a perfectly distinctive character, and are explainable only on the basis that the auricle is in a condition of continuous excitation. There is no return to the isoelectric line and no indication that the auricles are at any time electrically quiescent. The intrinsic deflections are followed by long extrinsic periods. Now the curves of the two cases of paroxysmal auricular tachycardia exhibit quite different characters. The auricular complexes, though grossly deformed in one case, are distinctly to be separated one from another and are easily recognizable as being periodically produced P-waves. In those instances in which the ventricular complexes do not interfere there is clearly a return of the curve to the isoelectric line. The mechanism underlying these arrhythmias cannot be the same as that responsible in auricular flutter.

*Auricular Fibrillation.*—Historical reviews and discussion of the various theories which have been advanced to explain the fundamental causes of this irregularity are to be found in the publications of Garrey<sup>6</sup>

TABLE I  
COMPARATOR ANALYSIS OF THE FLUTTER WAVES OF FIG. 16 (AVERAGE VALUES)

POSITION OF THE ELECTRODE		DURATION OF THE FLUTTER WAVE (SEC.)	TOTAL DURA- TION OF 3 SUCCESSIVE FLUTTER WAVES (SEC.)	TIME OF ONSET OF DESIGNATED (SEE FIG. 16) INTRINSIC DE- FLECTIONS AS COMPARED TO THE SUCCEEDING R-WAVE (SEC.)	TIME OF ONSET OF THE INTRINSIC DEFLECTIONS IN ESOPHAGEAL CURVES COM- PARED TO THE ONSET OF FLUTTER WAVES IN LEAD II OF A SIMULTANEOUS RECORD (SEC.)	
DEPTH FROM TEETH (IN CM.)	AS ILLU- STRATED IN FIGURE 4 A PART I3				PRECEDES BY	FOLLOWS BY
					0	0
Standard Lead II						
--	--	0.2065	0.6198	0.2591	0	0
30	Above C	0.2060	0.6194	0.2490	--	0.0102
32.5	B-C	0.2070	0.6202	0.2593	--	0.0044
34	D	0.2069	0.6200	0.2743	0.0150	--
36	E	0.2061	0.6191	0.2879	0.0294	--
38	F	0.2067	0.6204	0.2970	0.0380	--
40	G	0.2050	0.6208	0.3330	0.0734	--
42	Below G	0.2050	0.6210	0.3431	0.0860	--
Esophageal Lead						

and of Lewis.<sup>11</sup> A brief restatement of the more popularly accepted theories will satisfy the purposes of this report.

There is almost complete unanimity in the view that auricular flutter and auricular fibrillation are closely related, often interchangeable, and hence probably caused by variations in the operation of a similar underlying mechanism. The chief premises of debate are therefore largely concerned with theories and speculations as to the nature of the responsible mechanism. The main theories which still claim devotees are three in number. Common to all of them is the conception that a state of disturbance in the conductivity and the refractory phase of auricular musculature with the production of varying degrees of block is a prerequisite for the production of fibrillation.

The first theory, a modification or elaboration of the earlier views of McWilliam<sup>21</sup> and of Winterberg,<sup>35</sup> has been sponsored by Rothberger and Winterberg.<sup>30, 28</sup> It is variously known as the "tachysystole" or "polytopic" theory, depending upon whether one or several foci are assumed to be responsible for the continued, rapid excitation of the muscle. Closely allied to this explanation are those propounded by Hering<sup>9</sup> and Haberlandt,<sup>7</sup> who suggest that the responsible focus is the A-V node and by Scherf,<sup>32</sup> who postulates that the sino-auricular node may assume a similar rôle.

The second conception is that advocated by Garrey.<sup>6</sup> It is based on the experiments by himself, by Mines,<sup>23, 24</sup> and by the forerunners in the field of "circus motion," Romanes<sup>26</sup> and Mayer.<sup>20</sup> The theory follows the suggestion first made by Mines<sup>24</sup> that this mechanism might be responsible for paroxysmal tachycardia and fibrillation of the heart. Garrey<sup>6</sup> postulates that a provocative stimulus occurs under conditions favorable to the onset of fibrillation, that is, in the presence of factors interfering with the even and coordinated spread of the impulse throughout the heart muscle. In his own words<sup>5</sup> (p. 412): "From the point stimulated the impulses can spread in any and all directions, their progress being limited only by the preexistence or development of localized blocks within the tissue mass. Such blocks divert the impulse into other and more circuitous paths, and the area so blocked off can participate in contraction only when an impulse which has passed to other portions of the ventricle approaches it from another direction; this area thus in turn becomes the center from which the progress of contraction is continued, to be in its turn diverted by other blocks. . . . These conditions make possible the propagation of the contraction wave in a series of ringlike circuits of shifting locations and multiple complexity. It is in these 'circus contractions,' determined by the presence of blocks, that we see the essential phenomena of fibrillation." This theory, therefore, does not require that the excitatory impulse should be continuously repeated from the point of origin nor that there should be a single circulating or "mother" wave. The



process, once instituted, is, by this conception, capable of perpetuation even though the auricles should be separated from one another, for a possibility of multiple small secondary "circus movements" is envisaged which may serve as mobile reactivating foci in each large area of auricular muscle.<sup>6</sup>

The third theory is that propounded by Lewis<sup>11</sup> on the basis of researches pursued in his laboratory. The essential postulate of this theory is that in fibrillation, as in flutter, there is a rapidly circulating *single* central or "mother" wave which gives rise to centrifugal or "daughter" waves to the outlying parts of the auricle. Lewis holds that the parent wave may itself be blocked and obliged temporarily to adopt a new and sinuous pathway in a new plane but that it consistently retains its "circus" character, travels usually in a broadly delimited pathway and, if occasionally deviating, invariably returns to its original course which encircles the mouths of the great veins. He states<sup>11</sup> (p. 341): "*A priori* it is possible to conceive of circus movements of many types. We might even assume several circuits, completely or transiently independent of each other, and each controlling for a time material sections of the muscle; we might assume a single circuit wholly erratic in its course, looping widely in and out, sometimes breaking transiently into several circuits. *None of these views would meet the case of fibrillation as it exists clinically.\** There is more demonstrable order in the disorder than is consistent with one or other of these mechanisms." It is further held that the oscillations or "f" waves of electrocardiographic indirect leads from clinical cases are a measure of the prevailing rate of the "circus movement" in the auricle. These oscillations have also been studied by Lewis, Drury and Ilescu,<sup>15, 16</sup> who showed that a rotation of the electrical axis of each auricular "cycle" or oscillation through 360 degrees takes place both in auricular flutter and auricular fibrillation in man.

Of the three theories, that of Lewis today claims most adherents. It is particularly attractive, apart from the strong experimental evidence upon which it is based, because it supports a wide measure of clinical experience in linking auricular fibrillation with auricular flutter through an intermediary stage of impure flutter. Its application to cases of persistent auricular fibrillation is less clear, and the theory has been attacked by Rothberger,<sup>28, 29</sup> Garrey,<sup>6</sup> and more recently by Brams and Katz.<sup>2</sup> The latter have published evidence to prove that when the continuity of conduction of the fibrillating auricles is interrupted so as to divide the right auricle from the left both chambers continue to fibrillate. This, as well as certain experiments by Garrey,<sup>6</sup> are held to be unexplainable by the concept of a single central "mother" wave around the mouths of the great veins.

It is precisely because of the still considerable divergence of opinion on this subject that a brief restatement of the essential features of the

\*Italics ours.

various theories has been a necessary prelude to the presentation of additional evidence.

Of the entire series of 142 human subjects who have been investigated by the esophageal lead, 21 suffered from auricular fibrillation. Fourteen of these were earlier victims of rheumatic fever; 5 had severe arteriosclerosis and hypertension; and 2 were thyrotoxic. The majority of the cases had demonstrable (and in 5 great) dilatation of the left auricle. In these it was observed that the esophagus was displaced backward and to the right. This finding ensured that an electrode placed in the esophagus would not only be brought into even closer proximity to the surface of the auricle than normally is the case but also would be displaced toward the interauricular zone where a "mother" wave might be expected to have its location.

In the published curves of Lewis<sup>11</sup> (*Fig. 317*, p. 337), taken by direct leads from the exposed auricular surface of dogs in which auricu-

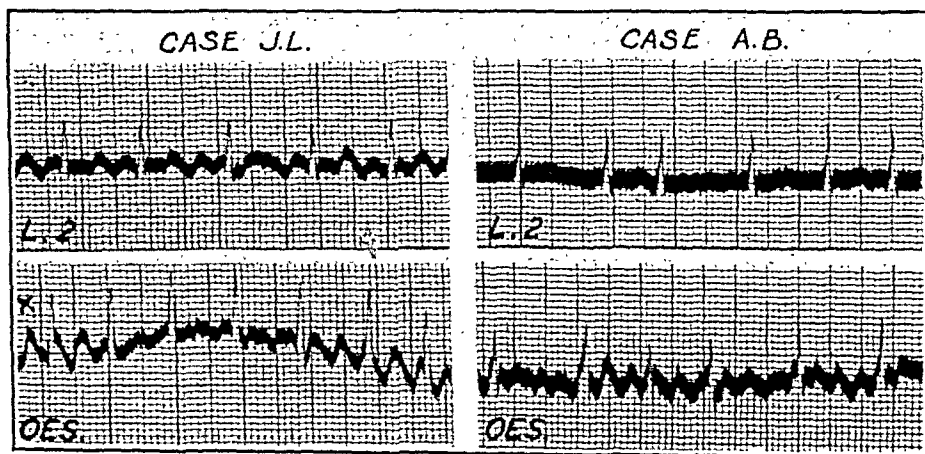


Fig. 17.—Patients J. L. and A. B. Records from two cases of auricular fibrillation. Lead II shown above in each case and esophageal records below.

Case J. L. Auricular fibrillation occurring in hyperthyroidism. The cross marks a doubtful example of intrinsic wave formation.

Case A. B. Auricular fibrillation occurring in rheumatic heart disease.

Standardization in both curves, 1 mv. = 10 mm.

lar fibrillation had been induced, definite intrinsic deflections are recorded. It has also been stated by Lewis<sup>11</sup> (p. 282) and implied by the published chest lead curves of Drury and Iliescu<sup>4</sup> from a human subject that if the electrodes could be brought closer to the surface of the heart of man the recorded "f" waves would be accentuated in amplitude and, presumably, in detailed form. That this is true in auricular flutter has already been demonstrated by esophageal electrograms showing excellent examples of intrinsic deflections. These facts and, in particular, the curves of Drury and Iliescu<sup>4</sup> from precordial leads seem to justify a confident anticipation that the application of the esophageal electrode to cases of clinical auricular fibrillation would yield records illustrating intrinsic deflections. Despite the operation of factors calculated to heighten the sensitivity of the esophageal lead, this expectation has been very rarely fulfilled.

Typical esophageal and conventional records are illustrated in Fig. 17. In only one instance in these curves is there the slightest trace of an intrinsic deflection. If the two cases of hyperthyroidism are excluded, the remaining 19 cases show an entire absence of intrinsic deflections. In all patients as many as seven esophageal records from as many auricular sites have been taken. Some patients (five) have been re-examined on separate occasions. In three subjects postural tests have been employed in an attempt to place the electrode nearer the inter-auricular zone. In 183 separate records of esophageal leads taken from these nineteen patients, there is no instance in which more than a moderate increase in the amplitude of the "f" waves has been observed; the oscillations, though often of considerably greater voltage, have invariably remained slurred and lacking intrinsic deflections.

In the two cases of hyperthyroidism the results were otherwise. Records from one of these patients in whom the irregularity had been present for over three years are shown in Fig. 17 (Case J. L.). The

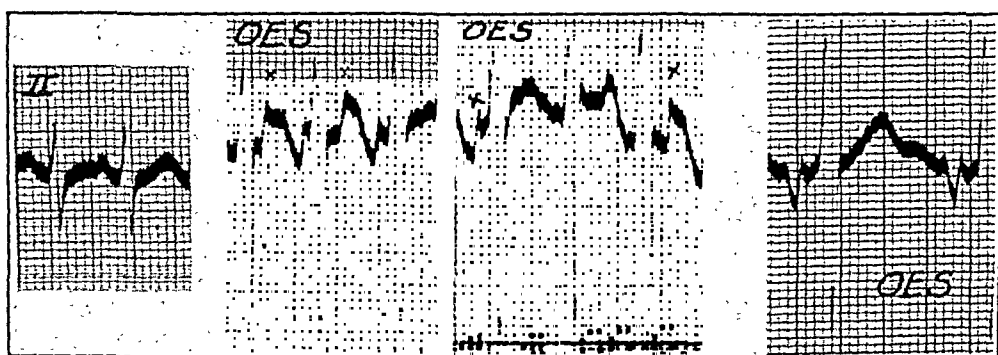


Fig. 18.—Patient M. G., a case of severe hyperthyroidism. The first three curves (Lead II and two esophageal records) were obtained when auricular fibrillation was present. Note the presence of intrinsic deflections as indicated by crosses. The last curve is an esophageal record obtained after spontaneous reversion to normal sinus rhythm following thyroidectomy. Note the deformity of the P-waves in the latter.

second case, a woman aged forty-two years, who had a basal metabolic rate of +71 and a history of auricular fibrillation for three months previous to examination, is of greater interest. The preoperative records of this patient are illustrated in Fig. 18, in which perfectly definite examples of occasionally occurring intrinsic waves are present. The last record of Fig. 18 shows an esophageal electrogram from the same patient obtained when normal sequential rhythm spontaneously appeared following thyroidectomy.

The two cases of auricular fibrillation in hyperthyroidism prove that the method is capable of detecting intrinsic deflections when they occur. Such deflections must represent the activation of a fairly substantial part of the auricular muscle in a locally coordinated manner. The slurred form of the recorded oscillations obtained in cases which show no intrinsic deflections is probably attributable to a fine division of the excitatory wave traveling in areas characterized by local blocks of great complexity.

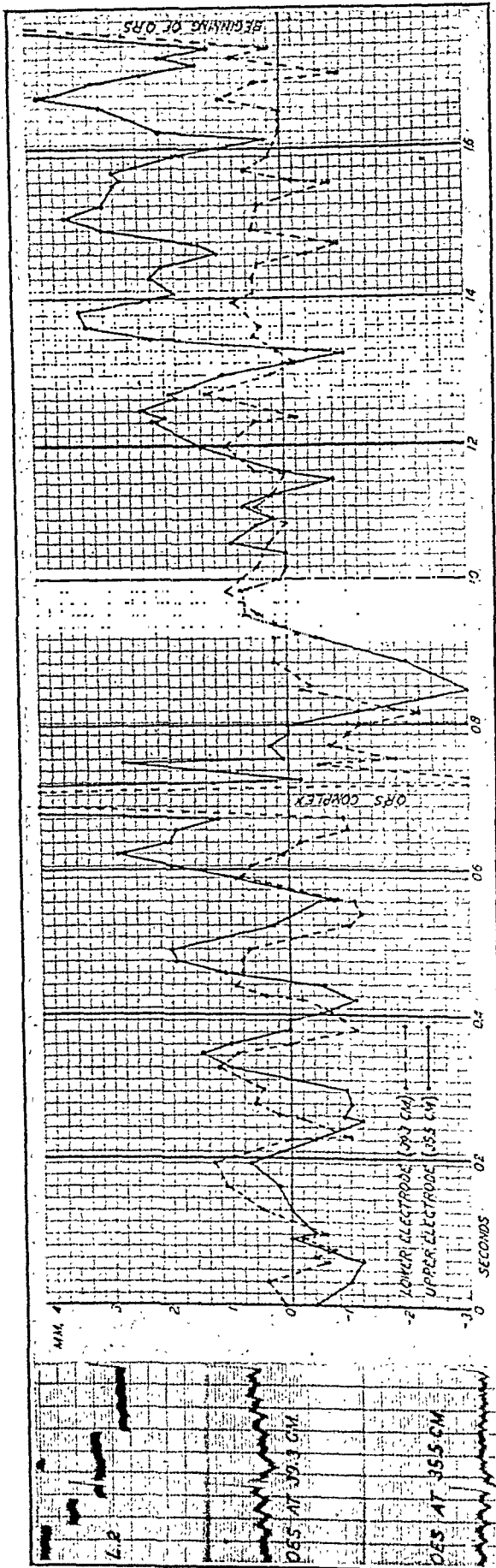


Fig. 19.—Patient C. B. The curves at the left were obtained as described in the text by the simultaneous recording of Lead II and two separate esophageal leads at the depth of 39.3 cm. and 35.5 cm. from the teeth. The latter have been analyzed by the comparator and graphically represented. The ordinates indicate time in seconds, the ordinates height of the deflections in millimeters. (For discussion, see text.)

In the section on flutter it was shown (Fig. 16 and Table I) that evidence of progressive excitation of the tissue in the left auricle underlying the esophagus was elicited. The peculiar time relationships of the intrinsic deflection for the various positions of the electrode were compared with the findings in the P-waves of normal cases, and the results were offered as evidence in support of Lewis'<sup>11</sup> version of the circus movement theory. An experiment was devised to investigate clinical auricular fibrillation along similar lines. An arteriosclerotic man aged sixty-six years, who showed only slight enlargement of the left auricle in the presence of auricular fibrillation, was selected. A double esophageal lead (see Part I, Fig. 5<sup>3</sup>) was passed until each electrode lay behind the left auricle. The electrodes were separated by a distance of 3.8 cm. Each esophageal electrode was attached to a right-arm terminal of a two-stringed Cambridge galvanometer. The left leg served as a site for the remote electrode in each instance. A single-string Hindle galvanometer was attached to the patient to record conventional Lead II. The resistances of all three circuits were balanced to obviate interference. By means of suitable prisms the movements of the three strings were recorded simultaneously.

Typical examples of the curves obtained from the patient under the above conditions are shown in Fig. 19. The esophageal electrograms of the recorded curves illustrated in Fig. 19 have been carefully measured with the comparator and plotted together on the basis of a common isoelectric line. The graph and the curves shown begin at a point 0.34 sec. after the foregoing QRS complex and are certainly free from ventricular effects at the time line marked 0.2 sec. An entire absence of intrinsic deflections is characteristic. The time relationships of the oscillations in the esophageal leads are clearly depicted in the graphical analysis of the curves. In the first part of the curves both electrodes have recorded oscillations of large amplitude lacking a sustained and ordered time relationship. After the QRS complex is written, the electrodes record much grosser differences in the form and occurrence of the "f" waves. The curves from the lower electrode are now finely segmented and of much smaller amplitude than those from the upper. Almost all semblance of order has disappeared, the onset of the smaller waves (lower electrode) occurring now before and now after the beginnings of the larger waves with frequent interpositional wavelets.

#### DISCUSSION

Similar results to those illustrated in Fig. 19 have been obtained in several records from the same and other patients. The absence of intrinsic deflections might conceivably be explained on the view that the esophageal electrode consistently failed to tap any part of the pathway of the "mother" wave. In view of the findings in flutter it is scarcely conceivable that, if a broader central circulating wave

were present in fibrillation, it would fail to give rise to occasional intrinsic deflections in 183 records from 19 cases. Argued on the basis of Lewis' theory<sup>11</sup> it seems necessary to postulate that at no time did the "mother" wave invade any tissue lying close to the electrodes. On the other hand, the changing character of the waves as illustrated in Fig. 19 could be partly explained on his theory by supposing that the plane of the "mother" wave had wandered farther from the lower electrode in the latter part of the record. But even this does not carry conviction, for it seems clear that any attempt to determine the direction of the electrical axes of such oscillations<sup>15, 16</sup> would be valueless in proving a central circus motion in this clinical case. A much more likely explanation would appear to be that at all of the investigated sites in nineteen cases the oscillations recorded by the esophageal electrode are the resultant of the total electrical potential variations in the areas closest to the electrode. This in turn implies that in these areas *multiple impulses* are traveling and giving rise to electrical vectors which by their sum or subtraction determine the movement of the galvanometric string. It follows that under the circumstances the number of such "f" waves could not be accepted as indicating the rate of circulation of a single "mother" wave.

The experimental work of Lewis<sup>14</sup> (see *Figs. 6-13*, inclusive) has proved that intrinsic deflections are obtainable by direct leads from the fibrillating auricles of dogs and that under these conditions there is strong evidence<sup>11</sup> that a single central circus movement is present. In these animals it is difficult to prevent spontaneous reversion to normal rhythm. In the only case of this series (Fig. 18) in which spontaneous reversion took place, intrinsic deflections have also been observed occurring singly or in a shortly consecutive order. If it were held that the formation of intrinsic deflections is characteristic only of the "mother" wave, then the pathway of the latter must, on this evidence, be considered to be a very devious example of "Umwandlung." Nevertheless, the example is important, for clearly the arguments of Lewis are applicable to this instance. It is quite possible that in this case a single central circus movement is present, that the direction of the electrical axis might be determinable, and that the predominant rate of the larger oscillations might represent the rate of the circulating "mother" wave. The case is one of severe thyrotoxicosis, a condition in which auricular flutter, impure flutter, and auricular fibrillation are quite commonly found. The question naturally arises whether the casual mechanism of auricular fibrillation in thyrotoxicosis, in paroxysmal attacks as well as in successful digitalis therapy in auricular flutter may not be exactly what Lewis postulated. Such cases quite frequently revert spontaneously from auricular fibrillation to normal rhythm. They resemble in this respect the characteristics of auricular

fibrillation artificially produced in experimental animals, but differ entirely from the common clinical examples of the irregularity which tend to persist.

In the present series no trace of an intrinsic deflection has been discovered in any example of *persistent* auricular fibrillation. It seems reasonable, therefore, to suspect that there may be a relationship between a tendency to spontaneous reversion, the presence of a single central circus movement, and the discovery of intrinsic deflections by semidirect leads. The results which have here been reported do not provide decisive evidence, but, when taken in conjunction with the experimental work of Garrey<sup>6</sup> and of Brams and Katz,<sup>2</sup> they are highly suggestive. They urge a reconsideration of the claims of a single "mother" wave as the responsible or enduring mechanism in persistently fibrillating patients. The results of the reported experiment (Fig. 19) are those which would be expected if (in accordance with Garrey's view) the single central wave had disintegrated into secondary, tenuous "circus motions" which serve as multiple, moving, and reactivating foci to the discoordinated muscle areas. Certainly there seems to be no good reason for supposing that this could not occur, and the suggestion is made that, if and when it takes place, the chances for spontaneous reversion to coordinated beating are thereby rendered remote. In other words, it is proposed that this development changes a case which tends spontaneously to revert to normal rhythm into a case in which a state of fibrillation remains obdurately persistent. It is further held that arguments based upon experimental animals which are with difficulty maintained in fibrillation are not strictly applicable to the *majority* of cases of auricular fibrillation as encountered in clinical medicine.

### *Summary of Section II*

The results of applying the esophageal lead in the study of three cases of auricular flutter are illustrated and discussed.

The three most generally accepted views of the mechanism underlying auricular fibrillation are briefly set forth.

The findings obtained in 21 cases of auricular fibrillation in which the esophageal method has been used are illustrated by typical curves and discussed.

A special investigation in a case of auricular fibrillation by means of a double esophageal electrode is described. The findings are analyzed and tentative conclusions are offered as to their significance.

### SUMMARY OF PART II

1. The results of employing the esophageal lead in an electrocardiographic study of auricular disorders in 92 human subjects have been recorded, analyzed and discussed.

2. The value of applying the method to patients exhibiting auricular abnormalities has been established.

3. Findings of particular interest have been obtained with reference to auricular arrhythmias (notably auricular tachycardia, auricular flutter, and auricular fibrillation).

#### GENERAL SUMMARY

1. The results of employing the esophageal lead in one hundred and forty-two human subjects have been analyzed in the light of practical and theoretical considerations. From both points of view, the lead has been proved to be a reliable and valuable electrocardiographic method of the semidirect type.

2. Interpretations of normal and abnormal esophageal curves have been supported by the results of animal experimentation.

3. The conclusions reached, after a study of a wide variety of clinical cardiac abnormalities, have been summarized under the appropriate headings.

4. Suggestions have been made as to the use of the method in clinical research.

In conclusion the author wishes to express his deep indebtedness to Dr. Edward P. Carter for his invaluable aid, advice and encouragement, to Dr. E. Cowles Andrus for his interest and help, and to Miss J. A. Vickers for her technical assistance in the recording and preparation of the electrocardiographic material, all of which have contributed immeasurably to the pursuit of this study. The writer's thanks are also due to the donor of the Bingham Fellowship without whose generous aid this investigation would have been impossible.

#### REFERENCES

1. Alexander, A. A., Knight, H. F., and White, P. D.: The Auricular Wave (P) of the Electrocardiogram: Clinical Observations With Special Reference to Pulmonic and Mitral Stenosis, *Arch. Int. Med.* 36: 717, 1925.
2. Brams, W. A., and Katz, L. N.: The Nature of Experimental Flutter and Fibrillation of the Heart, *AM. HEART J.* 7: 249, 1931-32.
3. Brown, W. Hurst: A Study of the Esophageal Lead in Clinical Electrocardiography: Part I. The Application of the Esophageal Lead to the Human Subject With Observations on the Ta-Wave, Extrasystoles, and Bundle-Branch Block, *AM. HEART J.* 12: 1, 1936.
4. Drury, A. N., and Iliescu, C. C.: Observations Upon Flutter and Fibrillation: Part VIII. The Electrocardiograms of Clinical Fibrillation, *Heart* 8: 171, 1921.
5. Garrey, W. E.: The Nature of the Fibrillary Contraction of the Heart—Its Relation to Tissue Mass and Form, *Am. J. Physiol.* 33: 397, 1914.
6. Garrey, W. E.: Auricular Fibrillation, *Physiol. Rev.* 4: 215, 1924.
7. Haberlandt, L.: Zur Entstehung des Herzflimmerns, *Ztschr. f. Biol.* 66: 327, 1916.
8. Hallock, P.: The Heart in Myxoedema With a Report of Two Cases, *AM. HEART J.* 9: 196, 1933-34.
9. Hering, H. E.: Der Sekundenherztod mit besonderer Berücksichtigung des Herzkammerflimmerns, Berlin, 1917, Julius Springer.
10. Leug, W.: Ueber das Elektrokardiogramms des Myxoedems, *Ztschr. f. klin. Med.* 104: 337, 1926.
11. Lewis, Sir Thomas: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw and Sons.
12. Lewis, T.: Irregularity of the Heart's Action in Horses and Its Relationship to Fibrillation of the Auricles in Experiment and to Complete Irregularity of the Human Heart, *Heart* 3: 161, 1911-12.



13. Lewis, T.: Observations Upon Flutter and Fibrillation: Part IV. Impure Flutter: Theory of Circus Movement, *Heart* 7: 293, 1918-20.
14. Lewis, T.: Observations Upon Flutter and Fibrillation: Part IX. The Nature of Auricular Fibrillation as It Occurs in Patients, *Heart* 8: 193, 1921.
15. Lewis, T., Drury, A. N., and Hiescu, C. C.: A Demonstration of Circus Movement in Clinical Flutter of the Auricles, *Heart* 8: 341, 1921.
16. Lewis, T., Drury, A. N., and Hiescu, C. C.: A Demonstration of Circus Movement in Clinical Fibrillation of the Auricles, *Heart* 8: 361, 1921.
17. Lewis, T., Feil, H. S., and Stroud, W. D.: Observations Upon Flutter and Fibrillation: Part II. The Nature of Auricular Flutter, *Heart* 7: 191, 1918-20.
18. Lewis, T., Meakins, J., and White, P. D.: The Excitatory Process in the Dog's Heart: Part I. The Auricles, *Phil. Trans. Roy. Soc.* 205: B, 375, 1914.
19. Lieberman, A., and Liberson, F.: An Internal Electrocardiographic Lead, *Proc. Soc. Exper. Biol. & Med.* 31: 441, 1934.
20. Mayer, A. G.: Rhythmical Pulsation in Scyphomedusae. Papers from the Tortugas Laboratories, Washington, D. C. 1: 115, 1908.
21. McWilliam, J. A.: Fibrillar Contraction of the Heart, *J. Physiol.* 8: 296, 1887.
22. Means, J., White, P. D., and Kranz, C.: Observations on the Heart in Myxoedema, *Boston M. & S. J.* 195: 455, 1926.
23. Mines, G. R.: On Dynamic Equilibrium in the Heart, *J. Physiol.* 46: 349, 1913.
24. Mines, G. R.: On Circulating Excitations in Heart Muscle and Their Possible Relation to Tachycardia and Fibrillation, *Tr. Roy. Soc. Canada* 8: Ser. 3, 43, 1914.
25. Pardee, H. E. B.: The Electrocardiograph as an Aid in the Diagnosis of Cardiac Valvular Disease, *J. A. M. A.* 78: 1250, 1917.
26. Romanes, G. J.: Preliminary Observations on the Locomotor System of Medusae, *Phil. Trans. Roy. Soc.* 166: 269, 1876.
27. Roos, J.: Auricular Fibrillation in the Domestic Animals, *Heart* 11: 1, 1924.
28. Rothberger, C. J.: Neue Theorien ueber Flimmern und Flattern, *Klin. Wehnschr.* 50: 82, 1922.
29. Rothberger, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, *Ergebn. d. Physiol.* 32: 472, 1931.
30. Rothberger, C. J., and Winterberg, H.: Ueber Vorhofflimmern und Vorhofflattern, *Arch. f. d. ges. Physiol.* 160: 42, 1914.
31. Samojloff, A., and Steshinsky, M.: Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralstenose, *München. med. Wehnschr.* 56: 1942, 1909.
32. Scherf, D.: Versuche zur Theorie des Vorhofflatterns und Vorhofflimmerns, *Ztschr. f. d. ges. exper. Med.* 61: 30, 1928.
33. Tung, C. L.: The Status of the Heart in Myxedema, *AM. HEART J.* 6: 734, 1931.
34. White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, *Arch. Int. Med.* 34: 529, 1924.
35. Winterberg, H.: Studien ueber Herzflimmern, *Arch. f. d. ges. Physiol.* 117: 223, 1907; 122: 361, 1908; 128: 471, 1909.
36. Zondek, H.: Das Myxoedemherz, *München. med. Wehnschr.* 65: 1180, 1918.

## UNUSUAL FEATURES OF TWO CASES OF SINO-AURICULAR BLOCK\*

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**S**INO-AURICULAR block is a rather rare finding in the clinic. For a long time the possibility of its existence was denied by eminent cardiologists (Lewis<sup>1</sup>) because in spite of many investigations (Thorel,<sup>2</sup> etc.) no specific pathway could be found between the sinus node and the auricular musculature. In animals S-A block has been produced by the so-called first Stannius ligature. Joachim<sup>3</sup> even succeeded in observing spontaneous S-A block during an experiment. But for a long time nobody saw this disorder in the mammalian heart, in which the anatomical structure of the sinus node is widely different from that of lower animals.

Finally by analyzing polygraphic curves, Mackenzie<sup>4</sup> and Wenkebach<sup>5</sup> showed clear evidence of the existence of S-A block in man. In addition to complete S-A block, which cannot be recognized electrocardiographically, Wenkebach distinguished two types of partial S-A block, which are analogous to Mobitz's<sup>6</sup> classification of partial A-V block. In Type 2 the P-P interval is practically uniform throughout the record, and after several normal P-QRS complexes one or more auricular waves (with the accompanying ventricular complexes) are dropped out. In this form of irregularity the basal rhythm is not altered, the pause forming a multiple of the P-P distance. In Type 1, the progressive form of S-A block, the P-P interval gradually increases, and after several complexes one or more P-QRS complexes are dropped out. In this form the pause is shorter than a multiple of the P-P distance. The explanation of this form is as follows: Sinus impulses, which of course cannot be seen in the curve, arise rhythmically. The first sinus impulse will be conducted to the auricle in normal time. Conductivity being impaired, the second impulse will reach the tired auricle a little more slowly. Later impulses will require a progressively longer time to reach the auricle. After several such cycles the conducting tissues will be completely exhausted, and the sinus impulse will fail to reach the auricle. Therefore, progressive increase of the P-P distance, followed by longer pauses, will be noticed in spite of normal impulse formation in the sinus node.

Many electrocardiographic records representing S-A block of Type 2 have been published, especially in the American literature, but the more interesting Type 1 is known only by venous curves, typical electrocardiographic records being unknown at present. The most important textbooks of electrocardiography, such as those of Lewis,<sup>1</sup> Clere,<sup>7</sup>

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Dressler<sup>8</sup> and Weber,<sup>9</sup> show no records of S-A block. Wenckebach and Winterberg,<sup>10</sup> in their atlas, show only one illustration of Type 1 block, published earlier by Edens.<sup>11</sup> Dressler, in his textbook presents only one case observed by Popper and Fischer.

Neither of these two cases is typical, however, for in the records the chief characteristic of Type 1 block, the progressive increase in the P-P distance, is absent. The authors presenting these two examples arrive at their conclusions only indirectly by assuming that in the case of Type 1 block *not the first*, but the *second* P-P interval, must be the shortest, therefore that progressive increase of P-P should begin only after the *second* P-P interval. Venous curves suggest this to be the rule, but the electrocardiographic records are not convincing because in the two cases cited the auricle drops out after each first or second P-P interval, consequently failing to show the law of progressive delay in conductivity for longer periods. Thus the sole assumption for which there are no convincing explanations, that in S-A block of Type 1

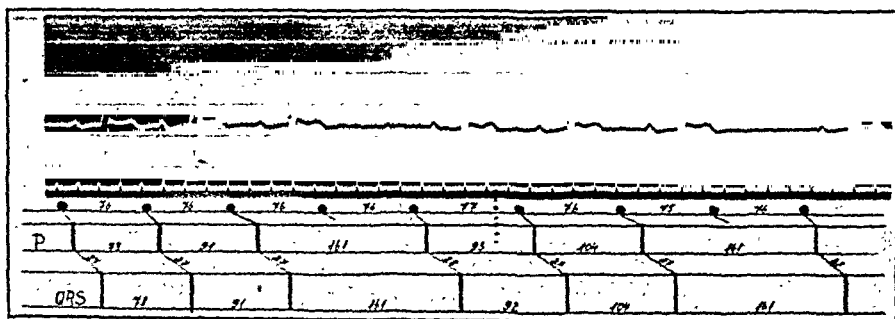


Fig. 1.—The upper line represents the supposed rhythmic formation of excitation in the sinus node (indicated by dots). Next line: gradual increasing of S-A conduction time, with no conduction after the third sinus impulse. P-line auricular waves. Next oblique line: Uniformly prolonged A-V conduction time. QRS line: ventricular contractions.

the second P-P interval is shorter than the first, leads these authors to assume the existence of S-A block of Type 1 in their electrocardiographic curves.

In this paper electrocardiographic records of two patients are presented. These show interesting points concerning both types of block. They are the first published records to show clearly (a) that in S-A block of Type 1 progressive delay in conductivity begins with the first cardiac cycle and persists over a rather long period (7 systoles) and (b) that progressive partial S-A block can coexist with progressive partial A-V block, a fact suggesting convincing evidence as to the mechanism of S-A block.

CASE 1.—G. S., a well-nourished woman, houseworker, thirty-one years old, complained of palpitation which had persisted for four years, increasing in the last three months. There were no other complaints except dysmenorrhea. There was no history of rheumatism or infectious disease; no evidence of arteriosclerosis or of focal infection (teeth, tonsils) could be found. Toxic effects of alcohol, nicotine, and lead could be excluded with certainty. Wassermann reaction and Kahn test were

negative. The blood picture was normal (red cells, 5,000,000; hemoglobin, 100 per cent; white cells, 6,400; differential—band forms, 2 per cent; segmented, 64; eosinophiles, 2; basophiles, 0; monocytes, 6; and lymphocytes 23 per cent). Physical and x-ray examination showed the heart to be of normal size. The sounds were clear and well accentuated, with no murmurs. The blood pressure was 125/70. There were no signs of decompensation. On auscultation and on palpation of the pulse the heart was found to be irregular, with a pause after each second or third beat.

The first record, taken Sept. 19, 1935 (Fig. 1), shows a longer pause not interrupted by P-waves, after each second or third "normal" complex. As sinus arrhythmia, ectopic rhythm, and blocked auricular extrasystoles can be ruled out, sino-

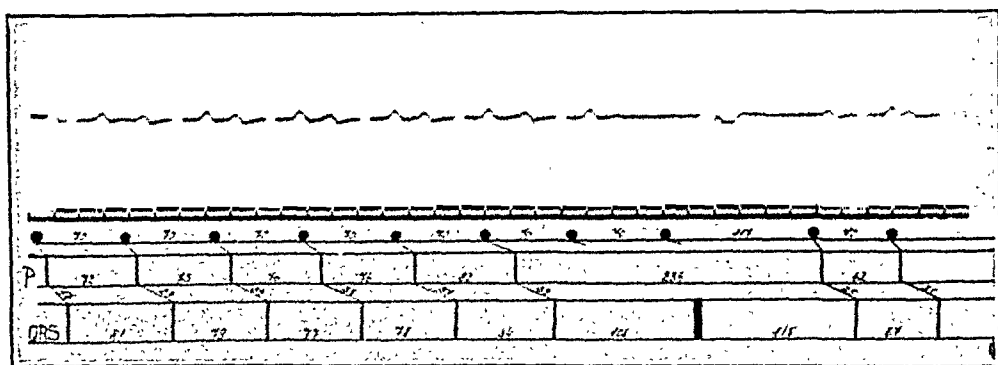


Fig. 2.—The upper line represents the supposed rhythmic formation of excitation in the sinus node (indicated by dots). Next oblique line: gradual increasing of S-A conduction time, with no conduction after the sixth sinus impulse. In the long pause a ventricular escaped beat is to be seen.

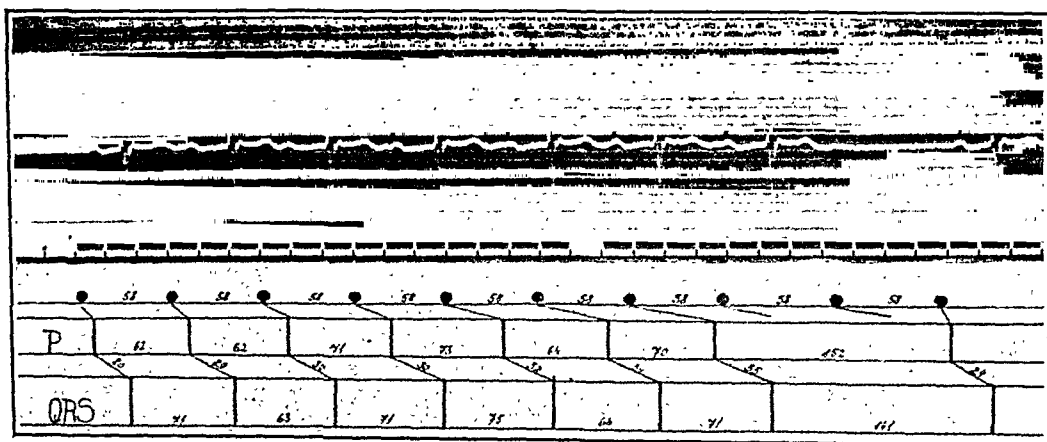


Fig. 3.—See Fig. 2. Dropped beat only after the seventh sinus impulse. No escaped beat. After the long pause the same periodicity begins again.

auricular block remains the only possible explanation. As the P-P intervals are gradually increasing before the pauses, the record is interpreted as belonging to Type 1, which interpretation is supported by later records. The P-R interval is 0.27 sec. (The very low voltage of the standard leads does not permit undisputed analysis of the record.)

The second record (Fig. 2), taken on September 28, shows sino-auricular block of Type 1. An auricular beat is dropped after every sixth complex; the P-P interval increases progressively from 0.72 to 0.82 sec. and the P-R interval increases from 0.17 to 0.39 sec. There are ventricular escaped beats in the long pauses. There is low voltage.\*

\*Lead II is shown, and the string is standardized so that 2 cm. represent 1mv.

The third record (Fig. 3), taken on October 8, shows a similar condition. After seven cardiac cycles a beat is dropped; the P-P interval increases from 0.62 to 0.70 sec.; and the P-R interval increases from 0.20 to 0.35 sec. There are no escaped beats.

*The basal metabolic rate was - 25 per cent and some weeks later was -33 per cent. Menstruation was painful.*

As to therapy, epherit decreased the frequency of dropped beats to some extent, but this effect was only transitory. Atropine (0.5 mg. hypodermically) produced the paradox reaction described by Eppinger and Hess<sup>12</sup> with an auricular or nodal ectopic rhythm and a bradycardia of 40 per minute. On giving thyroid tablets (0.10 gm. three times daily) for two weeks, the rhythm became regular for longer periods. When thyroid medication was omitted, the arrhythmia always reappeared but gave place to normal rhythm when the medication was again introduced. The patient now visits the clinic every week or so. She takes thyroid tablets periodically; she has normal sinus rhythm and no complaints.

*Discussion of Case 1.*—There are three principal points which justify the publication of this case:

1. After reviewing the literature it seems to be the first published case in which longer periods of the progressive form of S-A block are to be seen. From our figures it can be deduced that the generally accepted teaching according to which the first P-P interval must be longer than the second is not a general rule, for in our figures the P-P distance increases gradually from the first cycle to the last one before the pause. This regularity corresponds perfectly to theoretical considerations which gain a strong support from our records. The opposite observation, i.e., that the first P-P interval is longer than the second, appears to us to be exceptional and not in accord with theoretical possibilities.

2. In our case A-V conduction is impaired too. In Fig. 1 it is uniformly prolonged to 0.27 sec. The combination of S-A block of Type 2 (with constant P-P intervals) with uniformly prolonged A-V conduction is well recognized, having been described by Hewlett,<sup>13</sup> Korns.<sup>14</sup> Mackenzie,<sup>4</sup> Rihl,<sup>15</sup> Wallace and Katz,<sup>16</sup> and others, but the coexistence of the *progressive form* (Type 1) of S-A block with the *progressive form* (Wenckebach periodicity) of A-V conduction delay as illustrated in Fig. 2 and 3 has, we believe, not been recognized before. Nevertheless, it is not without importance, for, according to Wenckebach, the second type of heart-block is not surely a disorder of *conductivity*, but rather can be regarded as evidence of disturbed *contractility*, as disease of the musculature and not of the conducting system. In our case, however, the combination of definite defect of conductivity between sinus node and auricle and also a similar defect between auricle and ventricle proves with certainty that we have to do with no circumscribed lesion in some part of the heart musculature but that there is present a systemic disease affecting all conductive pathways. Figures 2 and 3 clearly illustrate the double Wenckebach periodicity in two different parts of the heart, between sinus node and auricle and between auricle and ventricle.

In the long pauses ventricular escaped beats arise and prevent the marked slowing of the pulse which would otherwise result from the coexistence of S-A and A-V conduction defect and which would be likely to cause serious disturbance of the general circulation.

3. All the electrocardiograms of this patient show low voltage. This fact is in accordance with the lowered basal metabolism. This is not a case of marked myxedema, for all skin symptoms and nervous signs are missing. Low basal metabolism and dysmenorrhea can more easily be referred to abnormal function of the hypophysis or to hypofunction of the adrenals, or to a combination of the two. It is well known that the adrenal cortex influences the gonads, and medullar hypofunction causes hypoadrenalemia, which leads to decreased sympathetic and increased vagus tone and which in turn may cause disturbance of conductivity in the heart.

According to most writers S-A block is rarely caused by anatomical lesions; more often—perhaps always—it is the expression of nervous or toxic influences. This interpretation must be extended to include hormonal disorders too.

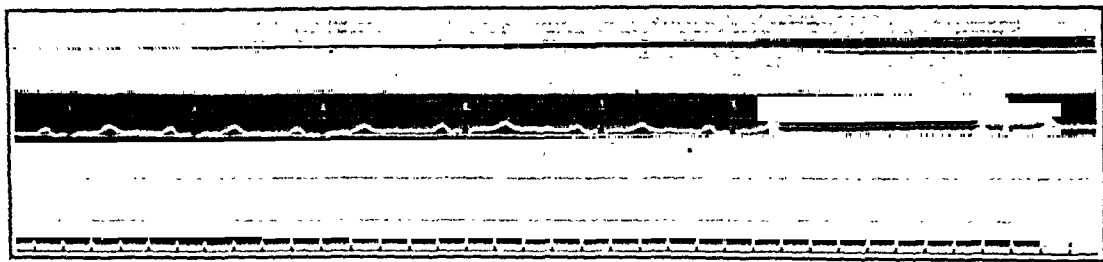


Fig. 4.—S-A block of Type 2. Constant P-P distances. Dropped beat after each sixth sinus impulse.

Nervous and endocrine troubles are always correlated with each other. Hormonal products influence the vagi and the accelerans, whose endings in turn later produce hormonal substances of cholinlike and adrenalinlike nature (Loewi,<sup>17</sup> Beznák<sup>18</sup>). Accordingly, the mechanism by which the two opposed representatives of the autonomic nervous system influences the underlying physiological units may be described as humoral (molecular) rather than neurophysical.

In this case digital compression of the vagi (carotid) and also holding the breath failed to have any effect on the arrhythmia. Emotion (fright) or bodily work (increased sympathetic tonus) suppressed the arrhythmia for some minutes, while epherit caused a diminished tendency to arrhythmia for longer periods and thyroid tablets were successful in maintaining regular rhythm as long as the medication was continued. This supports the view that hormonal disorders, disturbed neurohormonal equilibrium, were responsible for this rare form of arrhythmia.

A few months later we had the opportunity of observing another case of partial S-A block (Fig. 4). This record merits little attention for

it represents the common form (Type 2) with constant P-P intervals. Nevertheless, we consider that this case also is worthy of brief consideration because of the etiological factors, a cerebral tumor probably being responsible for the cardiac irregularity.

CASE 2.—The patient, a housewife, forty-two years old, appeared pale, undernourished, and nervous. She had no complaints referable to the heart. She had terrific headaches, visual disturbances, and serious psychic disorders, at times being completely disoriented.

On physical examination the heart was normal in size, the sounds were clear, and there was no hypertension or signs of decompensation. Cardiac irregularity was present, with regular intermittence after each sixth systole. The Babinsky phenomenon was present on the left side. Apart from this there were no other abnormal neurological findings in the motor or sensory field or in the reflexes. Ophthalmological examination, however, revealed choked disks in both eyes. On performing lumbar puncture cerebrospinal fluid appeared under high pressure. The height could not be determined because of the patient's restlessness. The cell count and all tests (Nonne-Appelt, Pandy, Weichbrodt, and Wassermann reactions, Kahn test, and colloidal gold curve) were normal. The next day encephalography was undertaken, but unfortunately the patient died within a few minutes after air was introduced. Permission for necropsy was refused by the family.

*Discussion of Case 2.*—In spite of the dearth of local and general signs and symptoms, we were inclined to assume that the patient had a brain tumor in the posterior fossa, because of the headaches radiating to the back of the neck, the symmetrical choked disks, the high intralumbar pressure, and the hypothetic vagus sign, S-A block. This latter assumption was strongly supported by the striking fact that after lumbar puncture the arrhythmia ceased promptly and regular rhythm persisted for some hours. Thus, while the presence of brain tumor could not be proved with certainty, the evidence (especially in the absence of other cardiac, toxic, or hormonal disorders) of (1) increased intracranial pressure, (2) cessation of cardiac arrhythmia after lumbar puncture, and (3) death of the patient when intracranial pressure was increased by the introduction of air, strongly support the view that elevated intracranial pressure was the cause of increased vagal tone which resulted in the S-A conduction defect and in the final fatal issue.

#### CONCLUSION

It has been shown that in the first case hormonal disorders influenced in a qualitatively identical manner the A-V conduction (i.e., genetic system) and the S-A conduction (common musculature). It seems unlikely that the same noxa should influence in the same way two tissue elements differing so widely from one another as do the genetic system and the common musculature. Lewis' interpretation seems to us to be more probable, namely that S-A block has its seat not *between* the sinus node and the auricular musculature, but *in* the sinus node itself, i.e., on its borders, from where excitation radiates synchronously in every direction to neighboring parts of the auricular musculature. Thus it

can be understood that a toxic agent traumatizes in the same manner two elements of the heart with different localization but with identical histological structure, the sinus node and the genetic system, which apparently are characterized by similar susceptibility toward extrinsic influences.

The second case, on the other hand, clearly illustrates the rôle played by purely mechanical factors, such as elevated intracranial pressure, in governing the action of the extracardiac nerves. Thus etiological factors, differing so widely from one another as do chemical (toxic or hormonal) and physical (nervous) disorders in the organism, can both lead to the same pathological process in the heart by way of the cardiac nerves. It matters not whether we consider the second type of heart-block as the result of conduction or of contraction disturbance, for the vagi act in the same manner upon conductivity and contractility.

#### SUMMARY

Two cases of sino-auricular block are presented. The first represents the rare form, the so-called Type 1, with progressively increasing conduction delay between the sinus node and auricular musculature, associated with progressively increasing A-V conduction delay. This trouble is ascribed to hormonal disorder, and the mechanism of S-A block is discussed.

The second case, in all probability, was caused by brain tumor, elevated intracranial pressure with consequent increased vagal tone causing S-A block of the so-called Type 2.

#### REFERENCES

1. Lewis: The Mechanism and Graphic Registration of the Heart-Beat, London, 1925.
2. Thorel: München. med. Wehnschr. 56: 2159, 1909.
3. Joachim: Deutsches Arch. f. klin. Med. 85: 373, 1905.
4. Mackenzie: Brit. M. J. 2: 1411, 1902.
5. Wenckebach: Arch. f. Anat. u. Physiol. (Physiol. Abt.) 297, 1906.
6. Mobitz: Ztschr. f. d. ges. exper. Path. 41: 180.
7. Clerc: Les arythmies en clinique, Paris, 1925.
8. Dressler: Klinische Elektrokardiographie, Wien, 1934.
9. Weber: Die Elektrokardiographie, Berlin, 1935.
10. Wenckebach and Winterberg: Unregelmässige Herzthätigkeit, Leipzig, 1927.
11. Edens: Deutsches Arch. f. klin. Med. 136: 207, 1921.
12. Eppinger and Hess: Ztschr. f. klin. Med. 68: 205, 1909.
13. Hewlett: Heart 10: 9, 1923.
14. Korns: Arch. Int. Med. 31: 15 and 36, 1923.
15. Rihl: Deutsches Arch. f. klin. Med. 94: 286, 1908.
16. Wallace and Katz: AM. HEART J. 6: 478, 1931.
17. Loewi: Pfüger's Arch. f. d. ges. Physiol. 189: 239, 1921.
18. Beznák: J. Physiol. 82: 129, 1934.



## ELECTROCARDIOGRAPHIC CHANGES IN HYPERPARATHYROIDISM\*

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ALTERATIONS in the electrocardiogram have been shown to occur in the hypocalcemia of tetany, but relatively few clinical observations have been made in the hypercalcemia of hyperparathyroidism.

Hecht<sup>1</sup> and Morgenstern<sup>2</sup> early called attention to the small QRS complexes and the prominent T-waves occurring in the electrocardiograms of patients with tetany. In addition to these findings, Doxiades<sup>3</sup> noted shortening of both the P-R and the QRS intervals. These changes were considered characteristic of hypocalcemia, but more recent reports (Salvadei and Pasoli,<sup>4</sup> and Marzahn<sup>5</sup>) indicate that such changes occur consistently in the electrocardiograms of relatively few patients. Unfortunately but little attention has been paid to the level of the calcium in the blood at the time the electrocardiographic studies were made.

Carter and Andrus<sup>6</sup> were the first to call attention to the prolongation of "electrical systole," or the Q-T interval, in hypocalcemia. This important observation was confirmed by White and Mudd,<sup>7</sup> and more recently by Marzahn.<sup>5</sup> Marzahn laid particular emphasis on the lengthened isoelectric period between the S-wave and the onset of the T-wave, and considered this to represent a tendency of the cardiac muscle to a tetanic state.

Numerous electrocardiographic studies have been made on animals following the intravenous injection of calcium chloride or the administration of parathyroid extract. These studies have been summarized by Berliner<sup>8</sup> and will not be reviewed in detail here. Following the administration to dogs of sufficient parathyroid extract to raise the level of calcium in the serum to 16 to 25 mg. per cent, Gold and Edwards<sup>9</sup> found that premature beats, shifts of the auricular pacemaker, alterations in the T-waves, and varying degrees of impairment of conduction occurred.

Segall and White<sup>10</sup> have reported a series of electrocardiographic studies of human subjects following the administration of calcium. In one patient no electrocardiographic changes occurred after the intravenous injection over a period of 15 minutes of 75 c.c. of 2 per cent calcium chloride solution. Following the daily ingestion of 15 to 24 gm. of calcium chloride for six days, inconsistent electrocardiographic changes appeared in eight of the eleven patients studied. In only one patient was consistent prolongation of the P-R interval noted. However,

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determinations of the concentration of calcium in the serum showed no alteration following the ingestion of such amounts of calcium in the one patient on whom such a determination was made. Measurements of the Q-T interval were not made.

Fujimori<sup>11</sup> has found consistent alterations in the electrocardiograms of fifteen patients following the intravenous administration over a period of two minutes of 20 to 30 c.c. of 3 per cent calcium chloride solution. The Q-T interval\* was shortened in all instances. In ten of the patients the P-R interval was appreciably lengthened. Decreases in the heights of the P-waves, QRS complexes and T-waves occurred consistently.

TABLE I

Measurements from electrocardiograms of two patients, before and after operation, with hyperparathyroidism. Both patients show a relatively short Q-T interval before operation, which became longer following surgery. The first patient shows a prolonged P-R interval before operation.

	DATE	R-R INTERVAL* (SEC.)	P-R INTERVAL* (SEC.)	Q-T INTERVAL* (SEC.)	K (Q-T INT.) ( $\sqrt{R-R}$ INT.)	SERUM CALCIUM (MG. PER 100 C.C.)
Case 1 V. F., a seven- teen-year-old girl	Jan. 23, 1934	0.66	0.23	0.30	0.371	19.2
	Jan. 31, 1934	Removal of adenoma of parathyroid gland				
	Feb. 5, 1934	0.87	0.15	0.36	0.386	9.6
	Feb. 9, 1934	0.72	0.12	0.35	0.414	9.2
	Mar. 26, 1934	0.87	0.12	0.40	0.428	9.4
	May 15, 1935	0.80	0.14	0.36	0.407	10.1
Case 2 J. F., a twenty- three-year-old man	Mar. 2, 1934	1.12	0.17	0.33	0.312	17.5
	Mar. 19, 1934	Removal of adenoma of parathyroid gland				
	Mar. 24, 1934	1.03	0.17	0.36	0.355	10.0

\*Average of four consecutive measurements.

Ballin<sup>12</sup> has published the electrocardiograms taken before and after operation of a patient with hyperparathyroidism. Attention was called to the short S-T interval before operation, which lengthened following surgical removal of an adenoma of the parathyroid. Ballin suggested that this shortened S-T interval might provide an accurate clinical sign for the diagnosis of hyperparathyroidism, supplementing the usual determinations of serum calcium and measurements of chronaxie in patients with hyperparathyroidism.

In a further attempt to evaluate the changes of the electrocardiogram in hyperparathyroidism, serial tracings were made of two patients before and after the surgical removal of an adenoma of the

\*Measurements of the Q-T intervals were not corrected for changes in the cardiac rate, which has been shown to influence greatly the Q-T interval. However, when such corrections are made, the Q-T interval is found to be shortened an average of 20 per cent in the fifteen patients studied.

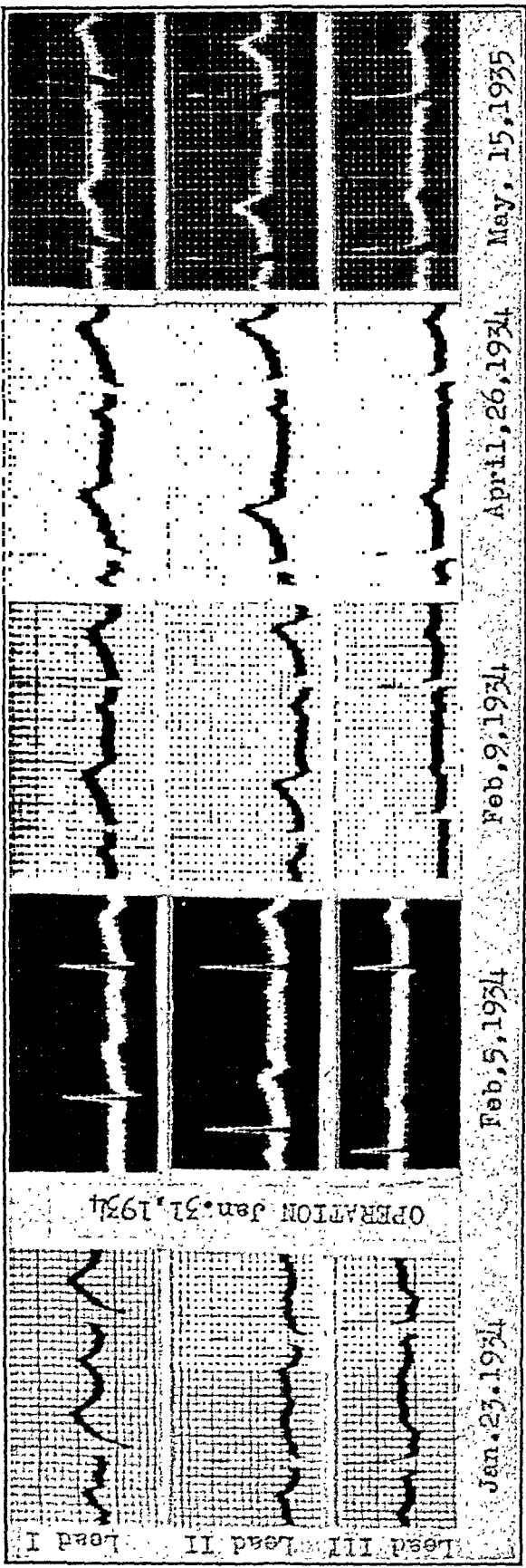


Fig. 1.—Serial electrocardiograms of the first patient (Case 1) before and after surgical removal of a parathyroid adenoma. Note progressive changes in T-waves following operation. Interval between time-marker lines equals 0.04 sec.

parathyroid gland. Both patients had osteitis fibrosa cystica and other findings typical of hyperparathyroidism. As the case reports of these patients are to be presented in a separate paper<sup>13</sup> on hyperparathyroidism, the clinical details will be omitted here.

#### ELECTROCARDIOGRAPHIC STUDIES

The electrocardiograms of these two patients, brother and sister, before and after operation, are shown in Figs. 1 and 2. The time relationships, together with determinations of the calcium in the serum, are shown in Table I. The column of figures under the heading, *K*, needs explanation. Bazett<sup>14</sup> and Cheer and Li<sup>15</sup> have shown that the Q-T interval is proportional to the square root of the pulse-period or the

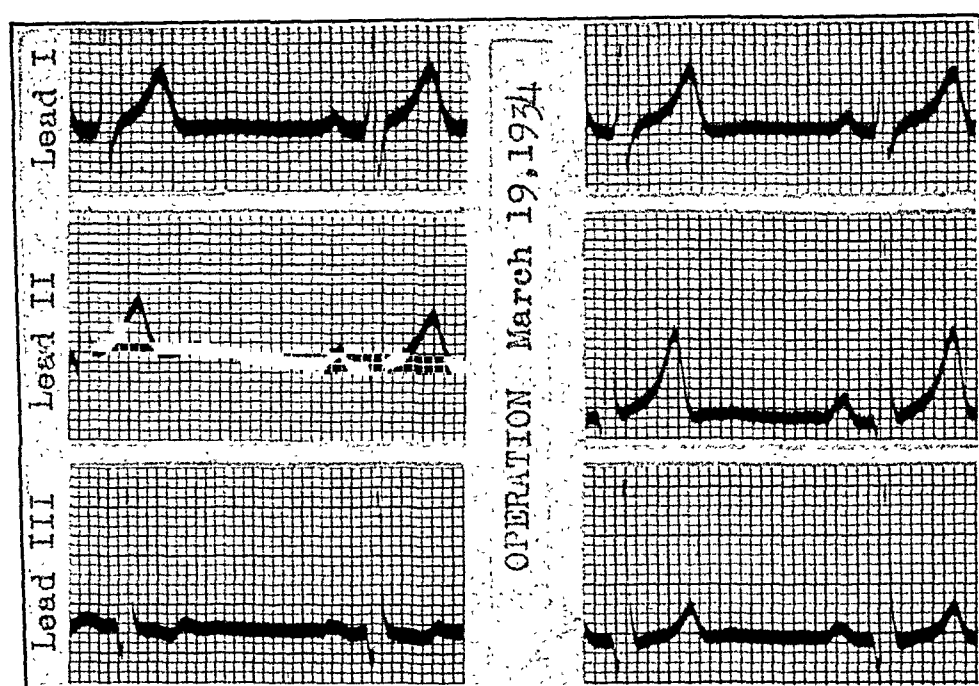


Fig. 2.—Electrocardiograms of the second patient (Case 2) before and after surgical removal of a parathyroid adenoma. Interval between time-marker lines equals 0.04 sec.

R-R interval. Thus, values for *K* were obtained from the equation  $K = \frac{\text{Q-T interval (sec.)}}{\sqrt{\text{R-R interval (sec.)}}}$ . Bazett found in males that  $K = 0.368 \pm 0.025$ , and in females that  $K = 0.399 \pm 0.040$ . In Chinese men, Cheer and Li found that  $K = 0.374 \pm 0.0012$ ; and in Chinese women,  $K = 0.388 \pm 0.0021$ .

Several noteworthy changes may be seen in the electrocardiograms of our first patient (Case 1), in whom the serum calcium was almost twice the normal amount. Before operation the auriculoventricular conduction time was abnormally prolonged; the QRS complexes were slightly slurred; the T-waves were abnormally low in Lead II; and the Q-T interval was shortened. Following operation, these deviations from the normal tended to disappear. Within five days the delayed auriculo-

ventricular conduction time and the slurring of the QRS complexes had disappeared; the T-waves in Lead II had become more prominent; the T-waves in Lead III were upright (formerly diphasic), but the T-waves in Lead I were less in amplitude than before. Minor changes in the T-waves continued to occur for several weeks, and the Q-T interval gradually became more prolonged.

Less pronounced changes may be seen in the electrocardiograms of the second patient (Case 2). Before operation the only abnormality was a short S-T interval. Following operation the T-waves became more prominent, and the Q-T interval became somewhat longer. No appreciable changes in the P-R interval or QRS complexes occurred.

It is of interest that the abnormal auriculoventricular and ventricular conduction, seen in Case 1, became normal soon after operation, whereas alterations in the Q-T interval and T-waves continued to occur for some time, although the calcium content of the serum had returned to a normal level.

#### COMMENT

The changes in auriculoventricular conduction time observed in the preoperative electrocardiogram of Case 1 resemble those found experimentally in dogs given parathyroid extract and those found by Fujimori in human subjects following the intravenous administration of calcium chloride.

Our studies, together with those of Ballin and Fujimori, confirm, as far as hyperparathyroidism and hypercalcemia are concerned, the observations of Carter and Andrus concerning the relationship of the Q-T interval to the calcium content of the serum.

Although shortening of the Q-T interval occurs consistently, it is doubtful if this sign is of much clinical value in the diagnosis of hyperparathyroidism, as the range of the Q-T intervals herein reported fall within the normal limits given by White and Mudd. If the formula of Bazett is used, the deviations from the normal appear more striking, but we doubt whether much significance can be attached to them.

#### SUMMARY

Serial electrocardiograms on two patients with hyperparathyroidism are reported, which showed shortened Q-T intervals (electrical systole) before operation. Following the removal of an adenoma of the parathyroid, the Q-T interval became longer in the electrocardiograms of each patient. Before operation one patient showed delayed auriculoventricular conduction and slurred ventricular complexes.

It is concluded that the shortening of the Q-T interval is not of sufficient degree to be of value in the clinical diagnosis of hyperparathyroidism.

## REFERENCES

- ✓ 1. Hecht, A. F.: Mechanismus der Herzaktion im Kindesalter, seine Physiologie und Pathologie, *Ergebn. d. inn. Med. u. Kinderh.* 11: 324, 1913.
- ✓ 2. Morgenstern, K.: Elektrokardiographische Untersuchungen über die Beziehungen des Herzmuskels zur Spasmophilie (Tetanie) im frühen Kindesalter, *Ztschr. f. Kinderh.* 11: 304, 1914.
- ✓ 3. Doxiades, L.: Konstitutionelle Schwäche des kardiovaskulären Systems im Kindesalter, *Ergebn. d. inn. Med. u. Kinderh.* 35: 98, 1929.
- ✓ 4. Salvadei, A., and Pasoli, E.: Cuore e tetania, *Lattante* 1: 665, 1930.
- ✓ 5. Marzahn, H.: Ueber eine Veränderung des S-T Intervalls im Elektrokardiogramm bei einem Fall von postoperativer Tetanie, *Ztschr. f. klin. Med.* 127: 182, 1934; 127: 367, 1934.
- ✓ 6. Carter, E. P., and Andrus, E. C.: Q-T Interval in Human Electrocardiogram in Absence of Cardiac Disease, *J. A. M. A.* 78: 1922, 1922.
- ✓ 7. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7: 387, 1929.
- ✓ 8. Berliner, K.: The Effect of Calcium on the Heart, *AM. HEART J.* 8: 548, 1933.
- ✓ 9. Gold, H., and Edwards, D. J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, *AM. HEART J.* 3: 45, 1927.
- ✓ 10. Segall, H. N., and White, P. D.: Clinical Observations on the Value of Calcium Chloride as a Diuretic, and Its Influence Upon the Circulatory Mechanism, *Am. J. M. Sc.* 170: 647, 1925.
- ✓ 11. Fujimori, K.: Clinical Investigation of the Influence of Calcium on the Circulatory System; the Influence of Calcium on the Electrocardiogram, *Acta scholae med. univ. imp. in Kioto* 16: 37, 1933.
12. Ballin, M.: Parathyroidism, *Ann. Surg.* 96: 649, 1932.
13. Goldman, L., and Smyth, F. S.: Hyperparathyroidism in Siblings, *Ann. Surg.* (In press.)
14. Bazett, H. C.: An Analysis of the Time-Relations of the Electrocardiogram, *Heart* 7: 353, 1920.
15. Cheer, S. N., and Li, R. C.: Studies on the Electrical Systole ("Q-T" interval) of the Heart: I. Duration of Electrical Systole in Normal Chinese, *Chinese J. Physiol.* 4: 191, 1930.

## Department of Clinical Reports

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### CARDIAC HYPERTROPHY IN A CASE OF COOLEY'S ANEMIA\*

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**A**NEMIA, experimental or clinical, has but rarely appeared and has been inadequately stressed in the literature as a sole cause of cardiac hypertrophy. In a survey of the causes of cardiac hypertrophy we had occasion to study the heart of a patient in whom at necropsy no causative factor for hypertrophy other than anemia could be found. The case was that of a nine-year-old boy with Cooley's anemia. We were interested in an attempt to derive the underlying mechanism responsible for cardiac hypertrophy in this case.

In the more recent literature, Whipple and Bradford<sup>1</sup> reported two instances of racial anemia with bone and pigment disturbances in two children, a brother and sister, which were similar to our case. The heart of their first patient, a child aged two years, weighed 155 gm. at necropsy and showed typical fatty degeneration. No mention was made of cardiac hypertrophy, and the muscle cells were regarded as normal, though the heart weight was more than double the normal for the child's age. In their second patient the heart was reported as enlarged to the left with a soft systolic murmur present. Necropsy, however, was not performed on this case.

Goldstein and Boas<sup>2</sup> reported diastolic murmurs and cardiac enlargement due to dilatation in anemia, and in one instance, unquestionable hypertrophy. Ball<sup>3</sup> reported cardiac enlargement in pernicious anemia. He had no necropsies, and it cannot be stated whether he was dealing with hypertrophy or with dilatation alone. Daniels and Burright<sup>4</sup> produced experimental anemia in rats by bleeding and observed definite hypertrophy of the muscle fibers of the heart. The weight of the desiccated specimen was found increased in comparison with the weight of the heart of a corresponding normal animal.

#### REPORT OF CASE

A nine-year-old boy was admitted to the hospital with a history of anemia of lifelong duration. The father and the mother were both Italians, living and well, and there were a brother eighteen years old, and a sister seventeen years old, also living and well. The patient had had measles at five years. Tonsillectomy and adenoidectomy had been performed two and one-half years before admission. At the time of operation an enlarged spleen was found. He was pale all his life. Occasionally he had complained of dyspnea after immoderate exertion and fatigue on ordinary exertion. Two days before admission, he developed pain in the left ear and the following day, a discharge from the ear.

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†Deceased, March 1, 1936.

Examination showed a mentally retarded boy with mongoloid facies, slanting eyes with small palpebral fissures, a sallow, *café-au-lait* color of the skin, bulging of the midportion of the frontal bone, and a saddle nose. There was a high arched narrow palate, and the chest was rachitic. The cervical vessels showed marked pulsations. A systolic thrill was felt over the right common carotid and subclavian vessels. The apex beat was in the fourth interspace just beyond the midclavicular line, and the heart was regarded as slightly enlarged. A soft blowing systolic murmur was heard over the apex, and a rough systolic murmur was present over the aortic region. The apical first sound was reduplicated. The abdomen was prominent. The lungs were clear. The liver was felt five fingerbreadths below the costal margin in the midclavicular line, the spleen, six fingerbreadths below the costal margin. Blood pressure was 104/52 on the right arm, and 88/52 on the left arm.

X-ray examination of the chest showed fairly marked dilatation of the heart. Electrocardiogram showed low voltage.

The blood count on admission was: hemoglobin, 30 per cent; red blood cells, 2.2 millions; white blood cells, 13,800. The differential count was, staff cells, 20 per cent; segmented cells, 54 per cent; small lymphocytes, 25 per cent; mononuclear cells, 1 per cent. Poikilocytosis, anisocytosis, and macrocytosis were present.

Radiographic study of the skeletal system showed the bone changes typical of hemoblastic anemia as given by Cooley.<sup>5</sup>

X-ray films of the mastoids showed cloudiness of the mastoid cells.

*Clinical Course.*—While he was in the hospital the hemoglobin level fell to 25 per cent and the number of red cells to 1.2 millions. He was transfused repeatedly and after the third transfusion developed a temperature of 104° F. The boy was discharged after a period of ten months, only to be readmitted four months later. At this time there was slight clubbing of the fingers and toes. The heart was enlarged, the rate rapid, and gallop rhythm was present. The liver edge was felt five fingerbreadths below the costal margin; the spleen was at the ilium; its anterior surface in the loins. A purpuric spot was present on the left shin. Blood count showed: hemoglobin 25 per cent; red cells 0.97 million; white cells 4,800. Serum albumin was 3.28 per cent and, serum globulin, 1.78 per cent. After a transfusion of 250 c.c. of blood, the red cell count increased to 1.46 millions. Shortly after another transfusion the temperature rose to 105.4° F., heart action and respiration became rapid, and he expired shortly thereafter.

*Necropsy.*—(Only the pertinent findings are reported.) There were 25 c.c. of fluid in the peritoneum. The spleen was considerably increased in size and extended in an oblique line from left costal margin and 2 in. below the umbilicus. The lower margin of the right lobe of the liver extended to the anterior superior iliac spine on the right side; the left lobe occupied the epigastrium, extending below to the umbilicus and above to the left parasternal line, meeting the spleen. The diaphragm was at the fourth intercostal space at both sides.

Heart: Measurements: weight, 200 gm.; aortic ring, 5 cm.; mitral ring, 8.5 cm.; pulmonic ring, 6 cm.; tricuspid ring, 9 cm.; left ventricular wall, 15 mm.; right ventricular wall, 4-5 mm. (The average heart weight for a nine-year-old child is 108 gm.) The epicardial fat was slightly icteric. The organ was moderately hypertrophied. The left ventricle, which usually forms not more than one third of the anterior surface, in this instance formed half of the anterior surface and the entire apex. The myocardium was pale red and flabby. The right auricle was moderately dilated but not hypertrophied, and the trabeculae carneae were flattened. The right ventricle was moderately dilated and hypertrophied. Both inflow and outflow tracts of the right ventricle were increased in length, particularly the latter. The pulmonic conus was slightly dilated. The left auricle was moderately dilated and slightly hypertrophied. The left ventricle was considerably hypertrophied and moderately



dilated, with considerable tigering of subendocardium. The leaflets were slightly icteric, but otherwise showed no abnormalities. The coronary arteries, sinuses, and veins were normal.

**Microscopic Findings of Heart:** Cloudy swelling and fragmentation of fibers. Cross-striations indistinct. Moderate amount of perivascular fibrosis. Muscle fibers hypertrophied. Nuclei hypertrophied. Lymphocytes and large mononuclear cells in interstitial tissue, usually where degeneration was most marked. A few of the nuclei gave faintly positive reaction for iron.

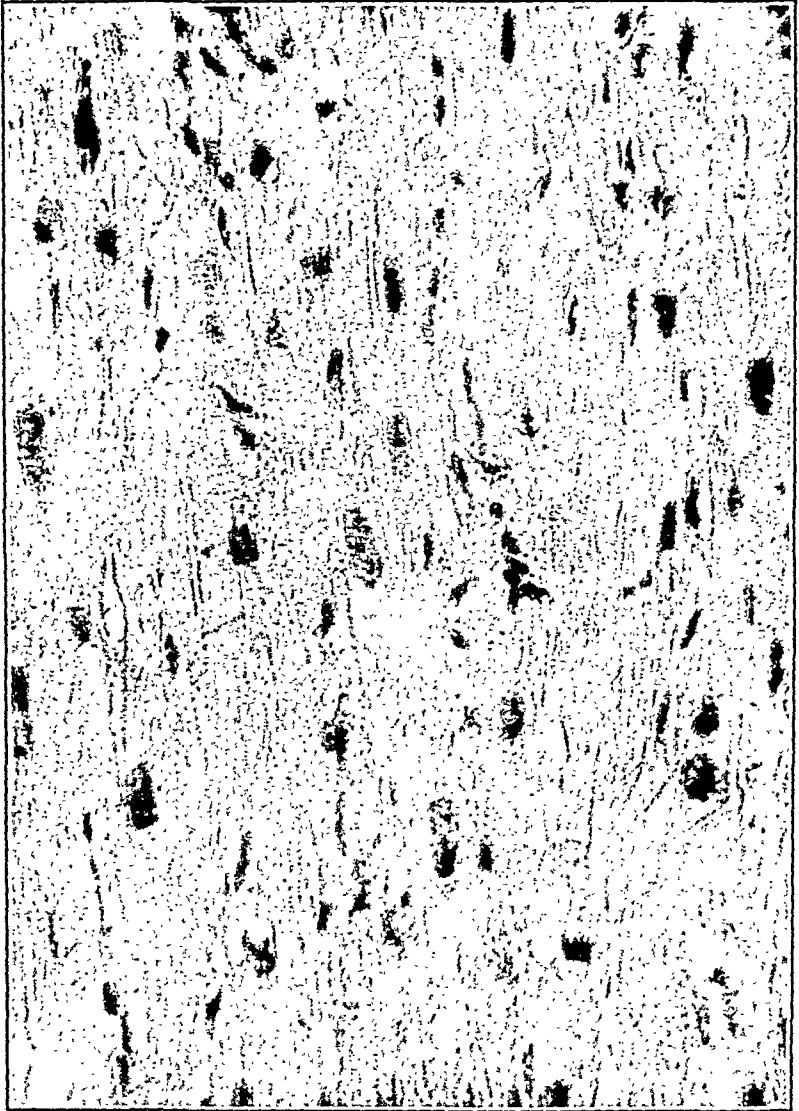


Fig. 1.—Photomicrograph, high power, showing cardiac hypertrophy.

Pulmonary arteries, veins, and bronchi were normal.

The liver, the spleen, and the skeletal system showed the findings common to cases of advanced hemoblastic anemia.

#### DISCUSSION

It is interesting to review some of the known physiological facts pertaining to cardiac hypertrophy and to inquire whether these facts furnish an explanation for cardiac hypertrophy in our case.

Frank,<sup>6</sup> supported by Straub<sup>7</sup> and by Wiggers,<sup>8</sup> held that the force of contraction of a muscle was dependent upon the initial tension to which it is subjected before contraction. Starling and his associates,<sup>9, 10</sup> however, contended that while, in general, initial fiber tension corresponded to initial fiber length, the efficiency of fiber contraction was determined solely by initial fiber length.

The mechanism whereby the heart does more work has been shown to be the same both in the normal and in the abnormal heart. Up to a certain point, increased fiber length is associated with a rise in intraventricular pressure and in the height of the isometric contraction curve. By increase of volume the normal heart, as shown by Starling and Visscher,<sup>11</sup> is capable of a wide range of augmented cardiac output and efficiency. With removal of the demand for increased work, the fiber resumes its normal size. However, when the heart has for a long time worked against increased resistance or heightened venous inflow, fatigue and a loss of muscle tone set in. Greater fiber stretching is then required to produce relatively small rises in intraventricular tension. With the persistence of fatigue, despite increasing diastole, both the tension and the isometric contraction curve actually fall.

The diseased heart in its response to work corresponds to the working of the nondiseased heart in fatigue, in that small increases of work require relatively large increments in fiber length. Increased fiber length, which in the normal heart is transitory only, in the diseased heart is usually chronic since cardiac enlargement is common in heart disease. This long-standing increased fiber length appears to be the stimulus in the diseased heart for muscular hypertrophy. The persistence of augmented fiber length results sooner or later, however, in dilatation from inadequate nutrition and insufficient oxygenation. Dilatation, if persistent, leads in turn to additional hypertrophy from increased diastolic stretching. A cycle of dilatation producing hypertrophy may repeat itself for a long time. Eventually, for some unknown reason in the metabolism of muscle, dilatation ceases to produce the stimulus for additional hypertrophy.

Both cardiac hypertrophy and dilatation have been observed experimentally in anemia. In our case long-standing severe anemia was present. Increase in volume, corresponding to increased fiber length, was known to exist clinically. Necropsy revealed also marked cardiac hypertrophy. In the absence of any other demonstrable factor, it seems reasonable to suspect that long-standing increased fiber length was the physiological stimulus for the cardiac hypertrophy observed. It is likely that the hypertrophy following dilatation resulted in maintaining the efficiency of the heart. With the persistence of severe anemia and anoxemia, however, the functional factors responsible for additional dilatation were present and produced even greater hypertrophy.

Decreasing oxygen saturation is associated with progressive cardiac dilatation. Dilatation increases the demand of the heart for oxygen. In our case, though the demand of the heart for oxygen was increased by dilatation, the severe anemia with diminished hemoglobin and the correspondingly reduced oxygen-carrying capacity may have led to a primary loss of contractility from inadequate oxygenation.\*

Hypertrophy produced a mechanical disadvantage since the blood supply was distributed over a relatively larger area. Oxygen absorption is known to be greater at slow than at fast pulse rates, and Harrison and his coworkers<sup>15</sup> have called attention to the fact that while the heart muscle of patients with heart disease is usually thicker than normal, the pulse rate is usually not correspondingly slower. Hypertrophy evidently may also be a contributory factor in producing a primary loss of contractility from nutritional insufficiency.

The occurrence of cardiac dilatation in severe anemia is well known. With this dilatation, increased fiber length or fiber tension, or both, are of necessity present and constitute the prime factors responsible for cardiac hypertrophy. Nevertheless, the development of cardiac hypertrophy is a rare occurrence in severe anemia. In other conditions, notably essential hypertension, particularly in women, and in chronic congestive failure due to arteriosclerotic heart disease, long-standing increased diastolic length and tension may be assumed. Similarly, in a considerable number of these cases, too, cardiac hypertrophy does not develop. Evidently in addition to long-standing increased diastolic length, there must be some other factor in the absence of which cardiac hypertrophy does not develop in a considerable percentage of cases of chronic congestive failure and in most cases of severe anemia.

#### SUMMARY

A case of severe anemia associated with cardiac hypertrophy is reported. The physiological factors responsible for cardiac hypertrophy are briefly discussed. An attempt is made to explain the cardiac hypertrophy in this case from a physiological point of view.

Cardiac hypertrophy is rare in anemia. Since dilatation is usually present in severe anemia and increased initial length may therefore be assumed, some factor other than chronically increased initial length must be present for cardiac hypertrophy to develop.

#### REFERENCES

1. Whipple, G. H., and Bradford, W. L.: Racial or Familial Anemia of Children Associated With Fundamental Disturbances of Bone and Pigment Metabolism, *Am. J. Dis. Child.* 44: 336, 1932.

\*It is interesting to note that anoxemia has been looked upon in the human heart as the underlying cause of angina pectoris. Herrick<sup>12</sup>, Coombs<sup>13</sup>, as well as Evans<sup>14</sup>, were of the opinion that cardiac pain in patients with pernicious anemia was out of proportion to cardiac sclerosis and considered anemia as a factor in the production of cardiac pain. The case of Goldstein and Boas<sup>2</sup> had not only anginal episodes, but cardiac hypertrophy as well with severe anemia.

2. Goldstein, B., and Boas, E. P.: Functional Diastolic Murmurs and Cardiac Enlargement in Severe Anemias, *Arch. Int. Med.* 39: 226, 1927.
3. Ball, D.: Change in Size of the Heart in Severe Anemia, *AM. HEART J.* 6: 517, 1931.
4. Daniels, A. L., and Burright, I.: Heart Weights of Normal and Anemic Animals, *Proc. Soc. Exper. Biol. & Med.* 30: 857, 1932-33.
5. Cooley, T. B., Witwer, E. R., and Lee, Pearl: Anemia in Children With Splenomegaly and Peculiar Changes in the Bones: Report of Cases, *Am. J. Dis. Child.* 34: 347, 1927.
6. Frank, Otto: Zur Dynamik des Herzmuskels, *Ztschr. f. Biol.* 14: 370, 1895.
7. Straub, H.: Dynamik des Säugetierherzens, *Deutsches Arch. f. klin. Med.* 115: 531, 1914.
8. Wiggers, C. J.: The Influence of Venous Return and Arterial Resistance on the Pressures Within the Right and Left Ventricles, *Proc. Soc. Exper. Biol. & Med.* 18: 144, 1920-21.
9. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, *J. Physiol.* 48: 357, 1914.
10. Patterson, S. W., Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, *J. Physiol.* 48: 465, 1914.
11. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, *J. Physiol.* 62: 243, 1926-27.
12. Herrick, J. B.: On the Combination of Angina Pectoris and Severe Anemia, *AM. HEART J.* 2: 351, 1926-27.
13. Coombs, C. F.: The Cardiac Symptoms of Pernicious Anemia, *Brit. M. J.* 2: 185, 1926.
14. Evans, T. S.: Cardiac Pain in Pernicious Anemia, *Brit. M. J.* 2: 638, 1926.
15. Harrison, T. R., Ashman, R., and Larson, R. M.: Congestive Heart Failure: Relationship Between Thickness of Cardiac Muscle Fiber and Optimum Rate of Heart, *Arch. Int. Med.* 49: 151, 1932.

## WIDELY PATENT FORAMEN OVALE\*

### CASE REPORT WITH DISCUSSION OF DIAGNOSIS

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COMPLETE anatomical closure of the foramen ovale, in the majority of cases, does not occur until the second postnatal year and in many instances it is delayed much beyond this period (Patten<sup>8</sup>). The general incidence of the probe-patent foramen ovale in individuals twenty years of age or over is approximately 23 per cent (Seib<sup>10</sup>) and can hardly be considered abnormal. A widely patent foramen ovale, however, is a rare congenital anomaly which gives rise to characteristic cardiovascular malformations. The embryological and the pathological features of auricular septal defects have been described in detail by Abbott.<sup>1</sup>

Roesler,<sup>9</sup> in an extensive review of the literature, found 62 cases with interatrial septal defects of 1 cm. or more. He gives a very complete summary and discussion of the clinical features, the pathological physiology, and the laboratory findings, and points out the following: (1) the average duration of life is thirty-six years; (2) three-quarters of the cases are complicated by other valvular lesions, the majority of which are mitral; (3) none is complicated by endocarditis; (4) all the hearts are large, and some are enormous, even in the absence of a valvular lesion, and this enlargement is due entirely, or almost entirely, to a right-sided dilatation which exceeds hypertrophy in a disproportionate degree; (5) the size of the heart is influenced by the size of the defect; (6) auricular fibrillation is common, thus distinguishing it from all other congenital cardiovascular malformations; (7) the five cases with electrocardiographic tracings all show definite right axis deviation, which, however, is marked in only one case.

Assmann<sup>4</sup> was the first to describe the characteristic roentgenological findings of a small aortic knob, prominent pulmonary conus, wide hilar vessels, and an enlarged, globular heart. McGinn and White<sup>7</sup> have summarized twenty-four cases in interauricular septal defect associated with mitral disease (Lutembacher's<sup>6</sup> disease). Similar cases have been reported.<sup>1, 2, 3, 5</sup>

The purpose of this presentation is to report a case of widely patent foramen ovale which illustrates the clinical, roentgenological and electrocardiographic peculiarities of this congenital defect.

#### REPORT OF CASE

I. G., a seventy-seven-year-old Hungarian born, white female, was admitted to the First Medical Division of Bellevue Hospital on the service of Dr. I. O. Woodruff

\*From the First Columbia Medical Division, Bellevue Hospital.

on Aug. 21, 1935, complaining of dyspnea, orthopnea, and substernal pain of six weeks' duration. The history was not entirely satisfactory because of language difficulty. The present illness started six weeks before admission with attacks of sharp, stabbing precordial pain which did not radiate and which was accompanied by dyspnea and orthopnea. Such episodes occurred with the patient at rest or very often were incited by exertion. Two weeks later, she first observed edema of the

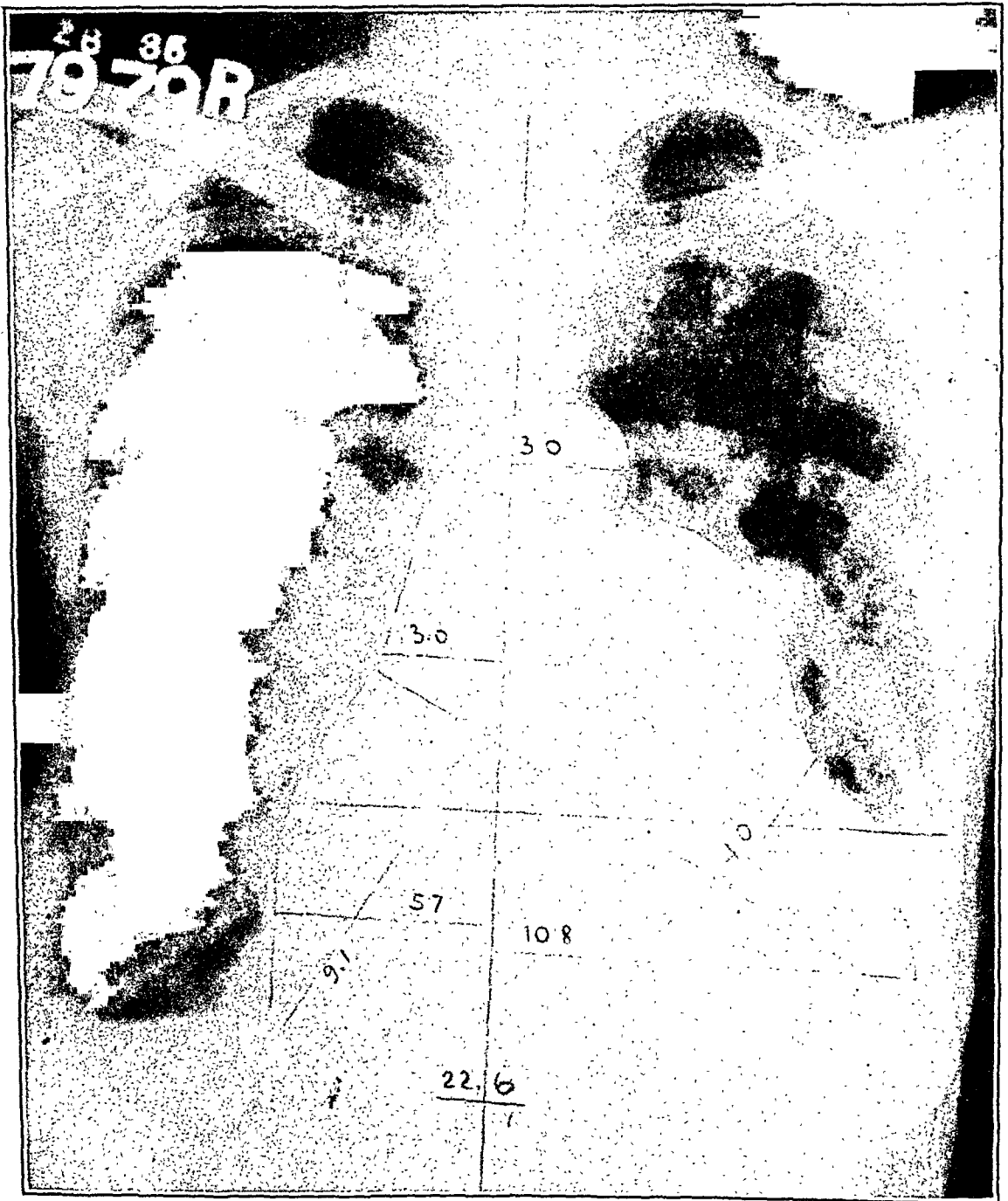


Fig. 1.—The upper half of the left cardiac border is formed by a large rounded pulmonary conus which is sharply offset from the calcified aortic knob superiorly, and from the left ventricle inferiorly. There are congestion and fibrosis at both hilar areas, which extends into bases. The cardiac apex is obscured. The aorta is within normal limits despite the presence of hypertension.

ankles which was progressive up to the time of her admission. The review of systems, past history, and family history was noncontributory.

The temperature was 99.2° F., the pulse 98, respirations 30, and blood pressure 140/110-100.

On admission the patient was noted as a small, poorly nourished and developed, old white female complaining bitterly of precordial pain. She was dyspneic, orthopneic, and cyanotic; noisy and unintelligent. The pupils were equal and reacted to light and in accommodation. Fundi showed advanced sclerotic changes. The mucous membranes were pale and cyanotic. Hearing was unimpaired. There was complete edentia. The lymphatic system was negative. The neck veins were slightly distended. The right breast was fuller and larger than the left, but no masses were felt. Resonance throughout both lungs was unimpaired. Many moist râles were heard over both bases. The apical impulse was palpable in the fifth space at the anterior axillary line. Conus dullness was definitely and markedly widened. A systolic thrill was easily palpable over the pulmonic area in the second interspace to the left of the sternum. The second pulmonic sound was accentuated and greater than the second aortic sound. A loud, rough systolic murmur was present over the pulmonic area. The second aortic sound and a soft systolic blow could be heard over the carotid arteries in the neck. A blowing systolic murmur of moderate intensity

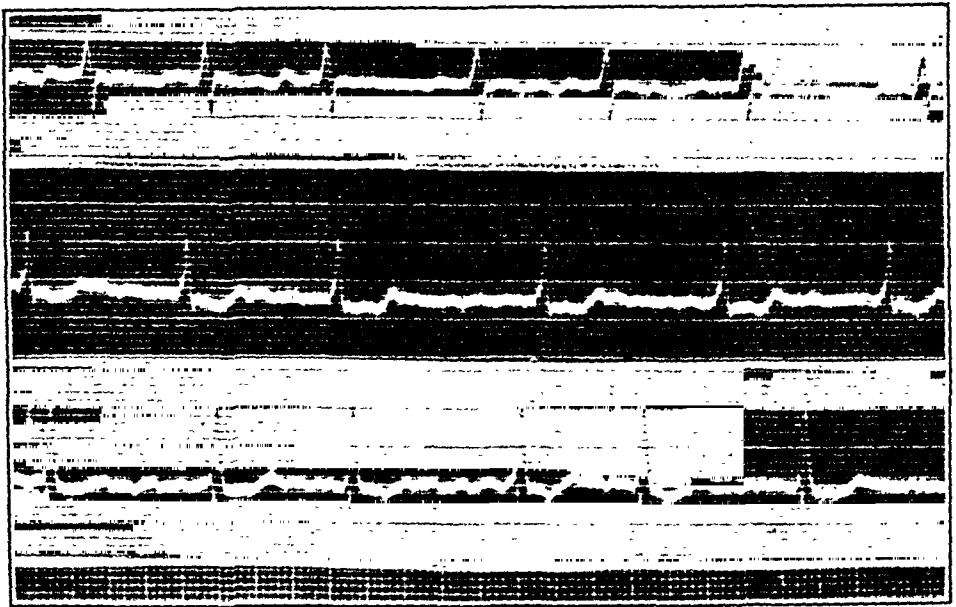


Fig. 2.—Auricular fibrillation with right axis deviation is present. The auricular oscillations are fairly coarse. The ventricular rate averages 75 per minute. The QRS interval is 0.08 sec.  $R_1$  and  $R_2$  are slurred. T is flat in Lead I, and upright in Lead II. The R-T segment is concave in Leads II and III.

was present at the apical area. The heart was irregular in rate, force, and rhythm, and there was a pulse deficit. The radial vessels were markedly sclerotic. A tender liver edge was palpable three fingerbreadths below the costal margin. There was pitting edema over the lower extremities extending to the midhigh. The fingers and toes showed no clubbing. Reflexes were physiological.

*Course.*—The patient responded very well to bed rest, diuretics, sedatives, and digitalis and was discharged after seven days to the Cardiac Clinic, which she failed to attend. On Sept. 21, 1935, one month later, she was readmitted complaining of precordial pain, dyspnea, and edema of the ankles. The blood pressure was 170/110. There was auricular fibrillation with rapid ventricular rate and a pulse deficit. Other signs were similar to those described upon the first admission. Symptomatic therapy was ineffective, and the patient expired on the third day after admission.

*Autopsy* (Performed by Dr. Schmidt, three hours after death).—The body was that of an adult white female, about seventy years of age, weighing about 130

pounds and appearing in fair state of general nutrition. Moderate amount of grayish hair was present upon the head and over the anterior pubes. Pupils were equal and regular, and conjunctivae, smooth and glistening. The nares and mouth were natural. The thyroid was not enlarged. The chest presented no abnormalities, and both breasts were small and atrophied; no masses were felt in either breast. The abdomen was somewhat distended, and there were several superficial, dilated veins in both upper quadrants. The extremities showed no cyanosis or clubbing, but there was considerable edema of both lower legs, extending from the ankles up to the knees.

On section, the subcutaneous fat was moderate in amount, and the musculature was flabby. The peritoneum was smooth and glistening and free of exudate. The abdominal cavity contained about 2,000 c.c. of thin, serous fluid, free from hemorrhage. The abdominal organs were apparently in their natural places.

*Chest:* The sternal plate was not removed owing to the limitation of permission to abdominal incision. It was determined, however, that no fluid was present in either pleural cavity.

*Lungs:* Both lungs were of natural size and somewhat heavier than normal. Visceral and parietal pleurae were quite separate, and the visceral pleura was glistening and free from exudate. There was a subminimal crepitation throughout. On section, homogeneous, dark red lung surface was revealed with a moderate amount of pigmentation. The surface was excessively moist, pitted upon pressure, and an excessive amount of blood and fluid could be expressed. Major and minor bronchi were natural.

*Heart* was greatly enlarged, weighing 505 gm. The pericardial cavity contained about 30 c.c. of thin, serous fluid, with no evidence of recent pericarditis. The pericardial surface on left anterior aspect of heart was roughened and had lost its normal glistening appearance. On opening the heart, it was found that the endocardium was smooth and glistening. The coronary sinus was somewhat dilated. The foramen ovale was patent, measuring 4 cm. in diameter. Edges were smooth. Tricuspid ring measured 13 cm., had a mild amount of sclerosis at the free margins. Chordae tendineae were thin and not fused. The right auricle appeared tremendously dilated. The pulmonic orifice measured 10 cm. Its cusps were three in number. A mild degree of fusion for about 2 mm. was found at the junction of the commissures. There was a mild degree of sclerosis at the free edge. The right ventricle was both dilated and hypertrophied, although the former condition was much more pronounced. The right ventricular chamber was approximately twice as large as the left. The right ventricular wall measured 6 mm. at the point of maximum thickness. Columnae carnae appeared flattened out. The pulmonary artery measured 10.5 cm. just distal to the pulmonic orifice, and a moderate number of yellowish plaques were present throughout. It was thin walled, dilated, and inelastic. The mitral orifice measured 8.5 cm. There was no fusion in the anterior and posterior cusps. There was a moderate amount of fatty, calcareous deposits in between the two cusps. There was no shortening or fusion of the chordae tendineae, although they appeared somewhat grayish and sclerotic. A moderate amount of sclerosis was seen along the free margin of the posterior cusp. The papillary muscles were somewhat hypertrophied, and the columnae carnae were only moderately flattened. The aortic orifice measured 7.5 cm., and the cusps were three in number. There was fusion at the commissural junctions for a distance of about 3 mm. There was some sclerosis at the base of the cusps. The left ventricular cavity was both hypertrophied and dilated, although the dilatation was very slight. The left ventricular wall measured 1.8 cm. at the point of maximum thickness. On section the cardiac muscle showed no fibrosis or fatty infiltration. Coronary ostia were patent, and traced throughout, showed a moderate amount of calcareous deposits in the wall



with visible encroachment upon the lumen. No thrombosis was seen, however. The inferior vena cava was dilated.

*Aorta* measured 6.7 cm. just distal to the aortic orifice, 6 cm. in the region of the arch, and 4.5 cm. in the region of the descending abdominal aorta. The ascending aorta is less than two-thirds the size of the pulmonary artery. Throughout, the wall was somewhat thicker than natural, had a reduced elasticity, and showed a moderate number of yellowish white plaques throughout. No calcification or ulceration was seen.

*Liver* weighed 1,450 gm. Its capsule was smooth and glistening. On section a homogeneous reddish brown liver tissue was seen. On pressure, an excessive amount of blood could be expressed. The gallbladder measured 7 cm., was free of stones,



Fig. 3.—A photograph of the right side of the heart illustrating the inferior vena cava and patent foramen ovale. Note the dilated and hypertrophied right ventricle and the large right auricle.

with its mucous membrane intact. The biliary radicles were natural. Hepatic artery and portal vein showed no change.

*Spleen* was small, weighing 100 gm. Capsule was thick and blue in color. On section, it was rather firm, dark red, with an edematous surface, from which an excessive amount of blood could be expressed. There were numerous whitish streaks seen on the cut surface. The splenic artery and vein showed no change.

*Pancreas* was of natural size and, seen from the surface, presented a grayish, lobulated appearance. On section the pancreatic tissue appeared small in amount and atrophied. There were no areas of fibrosis or neoplastic infiltration.

*Adrenals:* Both adrenals were small, and lay in natural position. Section revealed a rather well-preserved state of the cortex and medulla.

*Kidneys* both were of natural size and weighed 130 gm. each. The capsule stripped with ease, revealing a surface that was reddish in color with no visible or palpable granules. There were many areas of scarring on the kidney surface. On section, the cortex was demarcated from the medulla and measured 9 mm. The kidney felt rather firm and congested. The medulla was natural. The pelves, calyces, and ureters showed no changes.

*Bladder* was small, contained about 10 c.c. of urine. The mucous membrane was intact, and the openings of the ureters were patent.

*Gastrointestinal Tract:* Esophagus was thin walled, with no ulceration or stricture. The stomach was small and contained about 20 c.c. of undigested food material. There were no hemorrhages and no visible neoplastic or ulcerated areas. Pylorus was intact. Duodenum was natural. The remainder of the small intestine was thin walled and showed no change. Large intestine was natural, free from ulceration, newgrowth, and contained a moderate amount of dark yellow feces. Rectum and anus were without change.

*Genitals:* Uterus was small, atrophic, measuring  $2 \times 2$  cm. and was retroverted into the culdesac. The cervix was small and free of ulceration. On section, the uterine muscle appeared fibrotic and atrophic. The endometrium and cervical canal were atrophic. Tubes were thin walled, and the ovaries were small and atrophic and sclerotic.

*Head* was not examined.

#### DISCUSSION

The cardiovascular malformations secondary to a widely patent foramen ovale are probably best explained by the assumption that blood is shunted from the left to the right auricle. In accordance with Starling's law of the heart, the right auricle and ventricle dilate and become hypertrophied through the handling of an increased volume of blood. Because of the decreased volume of blood passing into the left ventricle and the arterial system, they become hypoplastic. The pathological physiology manifests itself clinically in the patient through pallor, a short stature, and a slight build. Cyanosis is usually not present until there is cardiac failure and the direction of the blood flow is reversed so that it flows from the right auricle to the left, "cyanosis tardive."

The physical signs as reported in the literature are extremely variable and their interpretations apparently impossible. In the case under discussion the hypertrophied conus arteriosus, dilated pulmonary artery, and increased pulmonary pressure might easily explain the accentuated pulmonic second sound, systolic thrill, and rough systolic murmur noted in the second interspace to the left of the sternum, just as these signs are found in mitral stenosis of a severe grade with marked conus enlargement. The fact that the auricles were fibrillating makes it fair to assume that they were incapable of producing such signs. Even if there had been a regular rhythm, it is hard to conceive of the auricular contraction causing a systolic thrill and a rough systolic murmur. It is interesting to note that despite a definite hypertension the electrocardiographic tracing shows the characteristic right axis deviation.

The exact cause for the cyanosis, enlarged liver, and edema is difficult to determine. Such signs frequently occur in the decompensated heart, and, though they have been described as typical of the failing heart with a large auricular defect, they are by no means pathognomonic.

#### SUMMARY

A case of widely patent foramen ovale in a female aged seventy-seven years is reported illustrating the characteristic physical signs, x-ray and electrocardiographic changes.

Among the features of a widely patent foramen ovale, the following may be listed:

1. Delicate physical make-up.
2. Cyanosis tardive.
3. Physical signs:
  - a. Large heart
  - b. Prominent conus
  - c. Unusual signs at the base (not common).
4. Roentgenological features:
  - a. Small aortic knob
  - b. Prominent pulmonary conus
  - c. Wide hilar vessels
  - d. Enlarged, globular heart.
5. Electrocardiographic findings:
  - a. Right axis deviation
  - b. Auricular fibrillation (relatively common).

This case further serves to illustrate the rather benign nature of a large interauricular septal defect when unaccompanied by a valvular lesion.

#### REFERENCES

1. Abbott, M. E.: Congenital Heart Disease, in Nelson's Loose Leaf Medicine, New York, 1929, Thomas Nelson and Sons, Vol. 4, pp. 226, 230, and 261.
2. Abbott, M. E., and Kaufmann, J.: Report of an Unusual Case of Congenital Cardiac Disease. Defect of the Upper Part of the Interauricular Septum (Persistent Ostium Secundum), *J. Path. & Bact.* 14: 525, 1910.
3. Amberg, S., and Willis, A. F.: Auricular Flutter With Congenital Heart Disease, *Am. J. Dis. Child.* 32: 99, 1926.
4. Assmann, H.: *Klinische Roentgendiagnostik der inneren Erkrankungen*, ed. 4, Leipzig, 1928, F. C. Vogel, p. 89.
5. Joules, H.: Aneurysmal Dilatation of Pulmonary Artery in Case of Congenital Heart Disease, *Lancet* 2: 1338, 1934.
6. Lutembacher, K.: De la stenose mitrale avec communication interauriculaire, *Arch. d. mal du coeur* 9: 237, 1916.  
Idem: La stenose mitrale avec communication interauriculaire, *Presse méd.* 33: 236, 1925.
7. McGinn, S., and White, P. D.: Interauricular Septal Defect Associated With Mitral Stenosis, *AM. HEART J.* 9: 1, 1933.
8. Patten, B. M.: The Closure of the Foramen Ovale, *Am. J. Anat.* 48: 19, 1931.
9. Roesler, H.: Interatrial Septal Defect, *Arch. Int. Med.* 54: 339, 1934.
10. Seib, G. A.: Incidence of Patent Foramen Ovale Cordis in Adult American Whites and American Negroes, *Am. J. Anat.* 55: 511, 1934.
11. Wahl, H. R., and Gard, R. L.: Aneurysm of Pulmonary Artery, *Surg. Gynec. Obst.* 52: 1129, 1931.

# MASSIVE CALCIFICATION OF THE MYOCARDIUM

## REPORT OF A CASE

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**M**ASSIVE calcification of the myocardium is a very rare condition, and one of which there are not more than a dozen available reports in the literature. The following case is of interest in that there was practically complete calcification of the anterior half of the left ventricle associated with occlusion of the descending ramus of the left coronary artery, the history indicating that this occlusion took place nine years before the death of the patient.

### CASE REPORT

J. W. G., a white male, aged fifty-eight years, complained of shortness of breath upon slight exertion and slight swelling of the legs during the day. At twenty-one years of age he had had inflammatory rheumatism, which left a stiff right wrist. Otherwise he enjoyed good health until September, 1926, when he was directing a crew of men in moving heavy books and equipment from the seventh floor of a building which had been so damaged by a tropical storm that the elevators could not be operated. While doing some heavy lifting during the rush, he felt something "tear in his heart." He became very weak and was unable to work and consulted a doctor who gave him treatment for heart disease. He returned to his home in Albany, Ga., in April, 1927, still weak and, according to the statement of his wife, colorless. During his illness he had continued to take digitalis prescribed at the time of his injury, which relieved a "little fullness" in his chest. During the next two years he rested, spending about eighteen hours a day in bed. Occasionally he would walk a block or two but this caused a "burning sensation in his chest, but no pain." This feeling was relieved by rest in a few minutes. In 1929 he regained his usual good color and normal weight and could walk a mile without difficulty. He had had no operations, no venereal disease.

When I first saw the patient in March, 1932, he stated that he had taken digitalis for five or six years and that it relieved a fullness in his chest better than did any drug that he had tried for the relief of pain. At this time he rested for a few days but soon felt very well and returned to his job as superintendent of a bus station. In November, 1934, I was again called to see him because of an attack of influenza. The attack was mild but left him so weak that he was unable to work for about two weeks. His health was fairly good except for a severe cough which digitalis did not relieve as well as it formerly had done. In February, 1935, he noticed considerable edema of his legs and dyspnea upon slight exertion, and he rested in bed for two weeks without consulting a doctor. He improved with rest and called at my office on March 4.

*Physical examination* at this time showed the cardiac impulse to be in the sixth space 1 inch outside the midclavicular line. The rate was 90; occasional premature contractions were present; blood pressure 125/85. (The patient stated that he never had had high blood pressure.) There were no murmurs, but on March 6 an intermittent gallop rhythm was noted. Moderate dullness and râles were present at the

right base. Liver dullness extended two fingerbreadths below the right costal border, and the patient complained of epigastric fullness as though he had eaten. There was moderate pitting edema of the shins. Orthopnea was never present, and, even when cardiac failure became more pronounced, the patient rested better without a pillow. The urine showed two-plus albumin with occasional hyaline casts.

*Subsequent Course.*—After this date the patient spent most of his time in bed, comfortable until August 1, when edema could no longer be relieved by rest, diuretics, and restricted fluids. He became progressively worse and died on Aug. 31, 1935.

*The Electrocardiogram* showed sinus tachycardia with rate of 130, occasional ventricular premature contractions.  $P_2$  was notched and P-R interval 0.18 sec. QRS group showed slurring of the downstroke in Lead I, prolongation to 0.12 sec., and left axis deviation.  $T_1$  showed high take-off and sharp inversion;  $T_2$  was upright; and  $T_3$  was sharply upright and greater than  $T_2$ .

*Clinical Diagnosis.*—*Etiological*, arteriosclerosis; *anatomical*, coronary sclerosis, coronary thrombosis and myocardial infarction; *physiological*, sinus mechanism, cardiac decompensation, anginal syndrome (?); *functional*, Class 3.

*Autopsy Findings of Heart.*—The pericardium was attached to all sides of the ventricles by numerous strong fibrous bands of adhesions. The whole anterior wall of the left ventricle was rigid, but appeared smooth and normal in shape. The percussion note was boardlike. X-ray examination of the removed specimen revealed a large area of calcification deposited in the anterior wall of the left ventricle and extensive calcification of both coronary arteries. Dr. Roy R. Kracke, of the Emory University Department of Pathology, examined the specimen and reported:

“The specimen consisted of a heart which had been fixed in formalin. It was of approximately normal shape. The pericardial surface, particularly on the anterior left ventricle, was markedly hemorrhagic with numerous petechiae and ecchymotic spots on the surface of the muscle. Also, on this same area were numerous fine fibrous adhesions. Sections of this area showed vascular channels which no doubt contributed a collateral blood supply to the left ventricle.

“The heart was slightly enlarged and weighed little more than a normal specimen. The weight was influenced by fixation to some extent. All valvular measurements were approximately normal. The aortic valve leaflets were smooth and pliable with good approximation at the commissures. The pulmonic valve was also normal. The edge of the mitral valve showed what is a questionable thickening and retraction of the free edge, although the line of closure was normal. This could have developed by fixation.

“The anterior half of the left ventricle was practically completely calcified, the area of calcification being hard, crackling, brittle, and white. It ranged in thickness from 0.5 cm. to only 3 mm. at its point of least thickness, which was near the apex. The calcified area measures 8 cm. in diameter since it is shaped like a half of a sphere. There is very little myocardial tissue in the area. The posterior half of the left ventricle is composed of normal myocardium with an occasional spot of fibrosis and calcification.

“The aorta about the coronary orifices shows a thickening with atheromatous plaques to the extent that there is almost complete closure of the left coronary opening. Examination of the left coronary shows a marked degree of calcification and intimal thickening along its entire length to the point of bifurcation where there is a complete calcified occlusion at the beginning of the anterior descending branch, with atrophy of that branch. This is an old lesion and was that which took place nine years before the death of the patient and which was followed by calcification of the part supplied by that branch.

“*Diagnosis.*—Massive calcification of the anterior left ventricle, following occlusion of the left coronary vessel at its bifurcation, this followed by development of collateral circulation through adhesions formed as a result of the infarction at that time.”

#### COMMENT

The case of calcification of the myocardium here reported is of interest because the process was so extensive as to involve the entire anterior half of the left ventricle, because the history extended over a period of nine years, and because vascular channels were demonstrated in the pericardial adhesions, a condition similar to that found in the cases reported by Beck, Tichy, Hirschboeck, and others.

#### REFERENCES

1. Beck, Claude S., and Tichy, V. L.: The Production of a Collateral Circulation to the Heart, *AM. HEART J.* 10: 849, 1935.
2. Moritz, Alan R., and Beck, Claude S.: The Production of a Collateral Circulation to the Heart, *AM. HEART J.* 10: 874, 1935.
3. Hirschboeck, F. J.: Calcification of the Myocardium Following Coronary Occlusion, *AM. HEART J.* 10: 264, 1934.
4. Moore, John J.: Myocardial Calcification, *Am. J. Roentgenol.* 31: 766, 1934.

# ACUTE BACTERIAL ENDOCARDITIS IN INFANTS

## REPORT OF A CASE

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CEDAR RAPIDS, IOWA

CASES of acute endocarditis in infants are not often reported in the medical literature, and the diagnosis is often not made until the necropsy. Most of these cases are associated with septic conditions in other parts of the body.

It is not our purpose to review the literature, since that has been done by others. One of the more recent reviews of this subject is given by Sansby and Larson.<sup>1</sup> They could find reports of only five cases in infants under seven months of age. They report a case in a boy five weeks old, which followed an attack of influenza of the mother. McCartney<sup>2</sup> suggests that the throat was the probable source of infection in his case. Other cases associated with septic conditions at birth have been reported in infants a few days old.

## CASE REPORT

This patient, a boy four months old, weighed 8 pounds and 3 ounces at birth. He was breast fed for three months and had been given supplemental feedings of milk during the fourth month. He had gained in weight normally and seemed entirely well until ten days before entering St. Luke's Hospital. At this time he refused the bottle for the first time and also had a slight cough. He was taken to the family physician who noticed a slight swelling in the region of the right parotid gland, which was suggestive of mumps. The temperature was normal, and the mother was instructed to return in a few days if the child was not improved. During the following week the mother noticed that the child had a mild fever at times but did not consider him very sick, although the glands of the neck were much larger. On the eighth day after the onset he was again taken to the family physician because of a high fever, which was found to be 105° F. One day before entrance to the hospital he was seen by one of us, who advised hospitalization and a thorough study of his condition.

On entrance to the hospital his temperature was 103.8° F.; the pulse was 130; and the respirations were 30. The following day the examinations of the otolaryngologist were negative except for the enlarged lymph glands of the right side of the neck, below the angle of the jaw and in the region of the parotid. X-ray studies of the sinuses and chest were negative. On the second day of the hospitalization the hemoglobin was 80 per cent; the red cells numbered 3,850,000; and the white count was 11,800. The urine on three examinations during the first two days was negative except for moderate amounts of acetone.

On the fourth day a few small petechiae were noticed beneath the nails of the toes and fingers. The pediatrician called in consultation suggested an x-ray study of the chest and long bones, but the report on these was negative. A blood culture grew many chains of *Streptococcus hemolyticus*. The physical examinations were negative except for the enlarged glands of the neck. The pulse was very rapid and

the fever varied from 101° to 105° F. The fever was the septic type, and death occurred on the eighth hospital day, seventeen days after the onset.

The necropsy, which was held a few hours after death, revealed many petechial hemorrhages in the skin and serous surfaces. The lymph nodes of the right side of the neck were enlarged, and those below the angle of the jaw were about 3 cm. across. The peritoneal cavity contained about 200 c.c. of clear straw-colored fluid. The lungs were congested but contained no abscesses or regions of consolidation. The heart weighed 43 gm. and many petechial hemorrhages were present in the pericardium. The right posterior aortic valve cusp was shortened and quite thick. Its surface was rough and covered with vegetations. These extended down on the endocardium of the left ventricle for a distance of about 5 mm. There were no evident changes in the other valves. The aortic and mitral valves are shown in Fig. 1. There were multiple recent infarcts in the spleen and kidneys.

The anatomical diagnosis was streptococcus septicemia with petechial hemorrhages in the skin and serous surfaces, infarcts of the spleen and kidneys, ulcerative endocarditis, and enlarged glands of the neck.

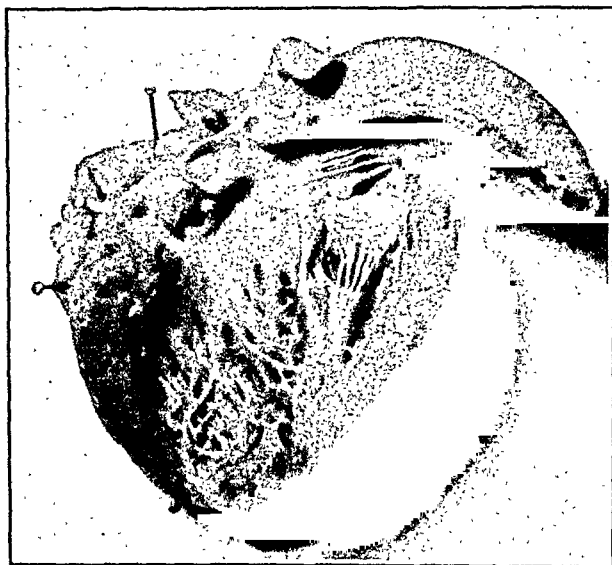


Fig. 1.

#### COMMENT

The symptoms in this case were those of sepsis, diagnosis of which was confirmed by the blood culture. Other foci of infection than those of the throat were sought in vain. Abnormal heart sounds were not heard on several examinations. The rapid rate of the heart and the low blood pressure in infants make it very difficult to detect disease of the heart valves in such cases. The throat was the apparent source of infection in this case.

#### REFERENCES

1. Sansby, J. M., and Larson, L. M.: Acute Bacterial Endocarditis in Infancy, *Am. J. Dis. Child.* 39: 1261, 1930.
2. McCartney, J. E.: A Case of Acute Ulcerative Endocarditis in a Child Aged Three and One-Half Weeks, *J. Path. & Bact.* 25: 277, 1922.



# Department of Reviews and Abstracts

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## Selected Abstracts

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Greene, Charles W.: The Nerve Control of the Coronary Vessels With New Experimental Evidence for the Pathways of Efferent Constrictor and Dilator Neurones in the Dog. *Am. J. Physiol.* 113: 361, 1935.

The data and discussions presented in this paper are condensed and briefed from a very large mass of observations on the dog. The illustrations are chosen for types and the protocols with each illustrate the method of comparison used. The major points are:

The efferent neurones to the coronary vessels are of the usual vascular antagonistic types of constrictors and dilators.

The coronary dilator neurones are of greater mass development, produce the more profound coronary reactions, and are more sensitive to stimulation.

The coronary dilator neurones are of thoracic spinal origin. They reach the heart chiefly via the stellate and the inferior cervical ganglia and the cardiac nerves arising from this region.

AUTHOR.

Kingisep, G.: The Wash-Out of Cardiac Glucosides From the Frog's Ventricle. *J. Pharmacol. & Exper. Therap.* 55: 377, 1935.

The author has investigated the reversibility of the action on the isolated and artificially stimulated frog's ventricle of the following drugs: (a) infusion of digitalis, (b) g-strophanthin, (c) ouabain, (d) digoxin, (e) seillaren, (f) k-strophanthin, (g) digitoxin.

In the case of all these drugs, washing-out produced recovery even after systolic arrest had been induced. The recovery was complete because a second intoxication followed exactly the same course as the first. The action was equally reversible when Ringer's solution or blood plasma was used, or when the drug was given to the intact frog and the arrested heart was excised and perfused. The ease with which the action could be reversed varied greatly with the different drugs.

The process of intoxication can be maintained by concentrations of glucoside far smaller than those needed to initiate intoxication.

The combination between glucosides and heart muscle resembles an adsorption process, but it is necessary to assume that hysteresis occurs.

AUTHOR.

Porter, W. B.: Diaphragmatic Flutter With Symptoms of Angina Pectoris. *J. A. M. A.* 106: 992, 1936.

The case reported is unique in that the movement of the minor contractions was recorded graphically and the rate was found to be 300 or more per minute, and a study of the diaphragm under the fluoroscope showed that the contractions were bilateral, spread over the entire diaphragm and apparently rhythmic in time and amplitude. The term "diaphragmatic flutter" is most appropriate and descriptive of the observed phenomenon.

There was associated with the disturbance of diaphragmatic function severe pain in the left pectoral muscle and in the left arm and hand over an area corresponding to the eighth cervical and the first, second and third dorsal segments of the cord. Over the area of referred pain there was marked hyperesthesia, which persisted even after relief from pain followed cessation of diaphragmatic flutter.

Experience with this patient suggests that there is a syndrome which is quite similar to angina pectoris and is directly related to a functional disturbance of the diaphragm. Just how much emphasis should be placed on the syndrome is difficult to decide. It is conceivable that disturbances of the diaphragm of a similar type to those observed in this patient may be more frequent than has been realized, for the clinical symptoms and physical phenomena are most elusive and it would be quite explicable for one to class a patient as a malingerer or conclude that a coronary accident had occurred while the true nature of the illness goes unrecognized.

The diagnosis may be further confused by temporary alterations in the electrocardiogram made during the peak of a paroxysm. Just how these changes are produced is difficult to conceive, unless there occur in the myocardium nutritional alterations. The disappearance of the changes with cessation of the diaphragmatic flutter suggests a direct relationship to the disturbance of diaphragmatic function.

Experience with this patient and others who suffered from lesser degrees of what was manifestly a similar clinical condition gives evidence that the most important differential diagnostic point between Heberden's angina and the "cardiodiaphragmatic syndrome" is that the latter condition is characterized by a notable absence of substernal pain and constriction, and there is a tendency on the part of the patient to be restless, which is in bold contrast to the fixity of one undergoing an episode of angina pectoris.

AUTHOR.

Smith, Carl H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children With the Use of Capillary Blood. *Am. J. M. Sc.* 192: 73, 1936.

A method of determining the sedimentation rate of erythrocytes has been presented which employs capillary blood and is suitable for use with infants and children. The tube that has been devised constitutes in effect a reduced macrosedimentation tube in that it embodies the basic requirements of apparatus in which sedimentation tests are carried out with venous blood. Close agreement was noted in 102 comparative determinations with the method, in addition to 128 other microsedimentation tests, using blood from the heel of the infant or finger of the older child and with a standard test utilizing venous blood.

With the microsedimentation method described in this study in which 5 per cent sodium citrate was employed as anticoagulant, the average rate of settling in normal infants and children was 4.2 mm. for one-half hour and 9.1 mm. for one hour, with respective ranges of 1 to 8 mm. and 3 to 13 mm. The single determination at the end of one hour was sufficient for comparative purposes. At the conclusion of the sedimentation test, the tubes were centrifuged for one-half hour at a speed of 2,500 revolutions per minute. The range of cell volume in the normal group was from 30 to 40 per cent for citrated blood (average, 35.8 per cent). In a small group of infants and children with various infections, 95 per cent showed cell volumes of 30 per cent for citrated blood (lower level of the normal group) and over. This minimal value is tentative and may require modification with more extensive investigation.

Since the determination of the sedimentation rate has been applied chiefly as a guide to infection, various procedures have been devised to correct for the factor of

anemia which in itself markedly influences the rate. While these methods are valuable, they are subject to the criticism that the test is thereby complicated and its availability for routine clinical use limited. It has, furthermore, been emphasized that moderate grades of anemia cannot be dissociated from infection and that they usually fluctuate together. In the light of these objections and of others that are discussed, it is suggested that wherever possible the cell volume percentage be reported together with the sedimentation rate. The rate of settling may then be evaluated in accordance with the extent to which the cell volume percentage approximates the range of normal, instead of substituting for it a value derived by comparison with an arbitrary standard.

AUTHOR.

**Adams, Wright: The Normal Duration of the Electrocardiographic Ventricular Complex.** *J. Clin. Investigation* 15: 335, 1936.

The most accurate formulas for the prediction of the duration of the electrocardiographic ventricular complex (Q-T time) from measurements of pulse interval in a series of 50 normal males and 54 normal females are: for males,

$$\overline{Q-T} = 0.1536 R-R + 0.2462,$$

and for females,

$$\overline{Q-T} = 0.1259 R-R - 0.2789,$$

in which Q-T = duration of electrocardiographic systole, and R-R = pulse interval. A table is provided which simplifies the use of these formulas.

The use of age, height, and weight of the individual, and height of the T-wave and axis of the electrocardiogram does not appreciably increase the accuracy of prediction of the duration of the electrocardiographic ventricular complex.

Other workers have found the duration of the electrocardiographic ventricular complex to be shorter for corresponding pulse rates. The reason for this difference is not apparent, but several possible explanations are discussed.

AUTHOR.

**Hamburger, Walter W., Katz, Louis N., and Saphir, Otto: Electrical Alternans.** *J. A. M. A.* 106: 902, 1936.

In a case of transient isolated electrical alternans, autopsy revealed an anomalous distribution of the right coronary artery with a calcified plaque markedly narrowing its mouth, generalized coronary arteriosclerosis, and multiple microscopic myocardial infarcts. In a second case of possible isolated electrical alternans, autopsy revealed multiple minute carcinomatous metastases within the myocardium and in the blood vessels of the heart. In the instance of alternans in auriculoventricular conduction no similar clinical report was found in the literature. It seems likely that the anatomical lesions in the first two instances, by leading to malnourishment of fractions of the heart, were responsible for the electrical alternans. They are, therefore, both of the coronary type of Kisch. The appearance of electrical alternans in instances in which the myocardial lesions are small and scattered may be significant.

A search of the literature revealed the rarity of isolated electrical alternans, the first case being the first described in this country and the first published with necropsy data.

The transitory nature of electrical alternans is demonstrated in our first case. There is a grave prognostic significance of electrical alternans.

While alternans of the heart may appear in several forms, there is evidence to show that fundamentally the mechanism is identical in all instances; namely, alternation of activity of portions of the heart. The form taken by the alternans will depend on the distribution of the alternating portions of the heart. The

transient character of electrical alternans emphasizes the need for closer scrutiny of electrocardiograms. The gravity of alternans and the fact that it sometimes appears only in the electrical form emphasizes the need of becoming more "alternans conscious." If more attention were paid to electrical alternans, probably many more instances would be found.

AUTHOR.

**Maher, Chauncey C.: The Effect of Two Water-Insoluble Squill Glucosids Upon the Electrocardiogram. Am. J. M. Sc. 192: 41, 1936.**

The effects of squill glucosides upon the electrocardiogram appeared to be characteristic and fairly consistent, particularly upon the R-T and S-T segments. The recorded changes of concavity and convexity produced were similar to those produced by digitalis as reported by Cohn and Pardee. In those patients whom we studied with both urginin and digitalis the changes produced were similar with equivalent amounts of each drug over equal periods of time.

There was a wide variation in the degree of effect produced in different patients, implying a variable amount of absorption of the ingested drug, a difference in the response of the patient, or other unknown factors.

In therapeutic doses, which is a relative term varying with each patient, the effects of urginin, like those of digitalis, appeared to be limited to an effect upon the R-T or S-T segment, slight prolongation of the P-R interval, and occasional extrasystoles.

In patients intolerant to the medication, the effects of overdosage appeared to be the production of frequent extrasystoles, marked prolongation of the P-R interval and the production of auricular fibrillation.

AUTHOR.

**Master, A. M., Jaffe, H. L., and Dack, S.: Undernutrition in the Treatment of Coronary Artery Disease (Particularly Thrombosis). Effect on the Basal Metabolism and Circulation. J. Clin. Investigation 15: 353, 1936.**

The effect of a low calorie diet (800 calories) on basal metabolism was studied in twenty-eight patients with coronary thrombosis and in fourteen with angina pectoris, whose control basal metabolic rate was within normal limits.

In thirty-one patients (74 per cent) the basal metabolic rate was lowered 15 to 35 per cent; such a drop was considered significant. In six patients, the basal metabolic rate fell 10 to 14 per cent, and in five, less than 10 per cent. The time required for the basal metabolism to drop was from two to four weeks. A similar period was required for its return to normal following the resumption of a regular diet. The body metabolism is determined for several weeks by the previous state of nutrition. Following a period of undernutrition, a subsequent period produces a more rapid and profound drop in basal metabolism. The loss of weight necessary to attain a significant fall in basal metabolism averaged 6 per cent of the initial body weight. The following factors tended to prevent a significant fall in basal metabolism: insufficient loss of weight, cardiac failure, upper respiratory infection, and repeated attacks of angina pectoris.

No ill effects resulted from the low metabolism induced by prolonged undernutrition of from three to twelve months' duration. The blood cholesterol, sugar, and protein were unaffected. Graduated increases in diet to 1,200, 1,500, and 2,000 calories often resulted in corresponding rises in basal metabolism. The drop in basal metabolism is not accompanied by such evidences of hypothyroidism as myxedema, diminished blood velocity, and hypercholesterolemia. Vital capacity is not affected.

The lowered basal metabolism had a beneficial effect on the cardiovascular system, resulting in slowing of the pulse rate, decrease in blood pressure and pulse pressure and diminution of the cardiac output and work of the heart. A low calorie diet often relieves the symptoms of heart disease.

AUTHOR.

Levy, Robert L., and Bruenn, Howard G.: *Acute, Fatal Coronary Insufficiency*  
J. A. M. A. 106: 1080, 1936.

There is a group of patients with atherosclerosis of the coronary arteries to whom death comes suddenly and in whose coronary vessels, at necropsy, no fresh thrombus is found. The syndrome may be designated "acute, fatal coronary insufficiency."

The clinical and pathological features of twenty-four cases falling into this category have been studied. Records of 352 other cases of coronary sclerosis, with and without thrombosis, have been similarly studied and used as a background for comparison.

In approximately 12 per cent of the fatal cases of coronary sclerosis without thrombosis, death occurred suddenly. If thrombosis had occurred, death was sudden in 33 per cent. The presence of thrombosis thus almost tripled the likelihood of sudden death. But thrombosis of a coronary artery was rarely if ever the immediate cause of death in these patients. It increased the liability to acute coronary insufficiency by further reducing the functional capacity of an already impaired coronary system.

Nonfatal attacks of various sorts in patients with coronary sclerosis may be regarded clinically as intermediate between the ordinary bout of anginal pain or its equivalent and a fatal seizure. It is probable that many of these attacks are due to minor degrees of acute coronary insufficiency without occlusion.

AUTHOR.

Willius, Fredrick A.: *Life Expectancy in Coronary Thrombosis*. J. A. M. A. 106: 1890, 1936.

In this study of 370 cases of coronary thrombosis, in 71.9 per cent the thrombosis occurred when the patients were between the ages of fifty and seventy years. No patients were less than thirty years of age; the incidence in the fourth decade of life was 1.6 per cent, while 17 per cent of the patients were in the fifth decade. There was a great predominance of males over females; the ratio was 7:1.

Solitary coronary occlusion occurred in 80.3 per cent of the cases; two episodes occurred in 17 per cent, three attacks in 2.2 per cent, and four episodes in 0.5 per cent of the cases.

Death directly attributable to the heart occurred in 51.6 per cent of the cases, while other diseases such as pneumonia, cancer, and nephritis accounted for the death of 2.7 per cent of patients. The patients surviving at the conclusion of the study comprised 45.7 per cent of the group.

Of the cardiac deaths 36.6 per cent were ascribable to coronary thrombosis; gradual cardiac failure accounted for 51.9 per cent, and sudden death of uncertain mechanism for 11.5 per cent.

While the incidence of females in this study was relatively small (12.4 per cent) their cardiac death rate was considerably greater than among males: females 63 per cent and males 50 per cent.

There was no correlation between the duration of pain in coronary thrombosis and death or survival.

The cardiac death rate increased progressively with recurrent coronary thrombosis. Among cases of solitary coronary occlusion the cardiac mortality was 47.5 per cent,

among cases in which there were two attacks 69.8 per cent, and among those in which three attacks occurred 75 per cent.

The patients living at conclusion of this study comprised 45.7 per cent of the group. Of these, 42.6 per cent reported themselves to be in good health, 23.1 per cent were well while living a restricted life, 28.9 per cent had recurrent anginal attacks, 3.6 per cent had congestive heart failure, and 1.8 per cent had had cerebral vascular accidents.

AUTHOR.

Alvarez-Moulia, A.: Congenital Stenosis of Aortic Orifice. Arch. urug. de med., cir. y especialid. 7: 499, 1935.

The author has had opportunities to study several cases of this congenital chronic disease in which most of the patients reached adulthood without their symptoms' needing special treatment. After a study of this disease some clinical, radiological and electrocardiographic symptoms may be added to the clinical picture already known.

The great clinical similarity of all the cases is striking. Each one shows the great degree of hypotrophy or aortic dwarfishness; this causes an inferior bodily development which would seem to be the result of the lesion's interfering with the blood supply of the great circulation. This interference constitutes an impediment for the development of organs during the growing period. The mental defectiveness, according to the author, is attributed to a pathogenic process resembling the former. There is, also, an hypotrophy of vessels revealed by the oscillographic study of the patients, due to the same pathogenic process to which the dwarfism is attributed.

The comparative examination of the electrical records obtained from the patients studied establishes fitting characteristics of the electrocardiograms. They will be:  $R_2$ ,  $R_1$ ,  $R_3$  form accompanied with "high tension or voltage" widening of the QRS space, slight crochetae of the R-wave in Lead III and above all as the most important element, an inversion of the ventricular deflection T in the three classic leads. These electrocardiographic signs have special interest since electrocardiograms obtained in the valvular diseases are more variable and contradictory.

The explanation of the stability of the different deflections, according to the author, is that the permanent intraventricular tension values have, on the whole, a great importance in the formation of the proper physiognomy of each electrical record. The continued action of the cardiac muscle from birth against the intraventricular tension causes an adaptation of its contracted state and tonicity. The ventricular preponderance, the muscular hypertrophy, and above all the special manner of the distribution of the final elements of the conduction apparatus will be in consequence to this. The latter elements of the "intraventricular conduction" will form the special type of electrocardiogram.

AUTHOR.

Sendroy, Julius, Jr., and Schultz, Mark P.: Studies of Ascorbic Acid and Rheumatic Fever. I. Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to the Study of Rheumatic Fever. J. Clin. Investigation 15: 369, 1936.

The urinary excretion test for the adequacy of ascorbic acid nutrition has been improved and placed upon a quantitative basis by a chemical and clinical study of the various factors affecting the final results. Applied to a comparison of patients with rheumatic fever and control subjects, the results of this method do not support the concept that a condition of ascorbic acid deficiency is a predisposing factor in the causation of this disease.

Through digestive disturbances, patients with rheumatic fever evidently may develop a real hypovitaminosis on an ordinarily adequate diet. One would expect in such patients that the tissues might be depleted not only of ascorbic acid but of other vitamins and essential food constituents of which there may not be large reserves in the body. However, even if we assume, contrary to the evidence of our experiments, that it is simply ascorbic acid deficiency that is associated with every case of rheumatic fever, it seems much more reasonable to regard the train of events, including digestive disturbances, leading to such depletion of the tissues, as caused by an infectious process, rather than to think of the ascorbic acid deficiency as initiating the infection. It seems certain that the factor of infection is present in all cases of rheumatic fever, whereas the signs of ascorbic acid subnutrition, if present, are probably incidental. Furthermore, it should be noted again that such signs of deficiency as have been found are only relative and not absolute. It has already been pointed out that the average results set up too high a standard of normality so that degrees of ascorbic acid deficiency, relative to the control patients previously on diets of about 100 mg. ascorbic acid daily, would be exaggerated in the direction of ratings too low for ascorbic acid nutrition. When all of these factors are taken into consideration, it is difficult to accept subclinical scurvy as an etiological agent in rheumatic fever.

AUTHOR.

Schultz, Mark P.: Studies of Ascorbic Acid and Rheumatic Fever. II. Test of Prophylactic and Therapeutic Action of Ascorbic Acid. *J. Clin. Investigation* 15: 385, 1936.

Two comparable groups of rheumatic children, one of them receiving daily doses of ascorbic acid, were observed at intervals during late winter and early spring. As indicated by tests of capillary permeability, the development of subclinical scurvy was prevented in the treated group, but the incidence of active rheumatic fever was not favorably affected by this medication.

The clinical manifestations of acute rheumatic fever were not demonstrably affected by the oral or intravenous administration of ascorbic acid over periods of several months. Large doses of orange juice were also ineffective.

These data are additional evidence that ascorbic acid deficiency is not a necessary factor in the etiology of rheumatic fever.

AUTHOR.

Pickering, G. W.: The Effect of Introducing Blood From Patients With Essential Hypertension Into Other Human Subjects. *Clin. Science* 2: 185, 1936.

The changes in arterial blood pressure produced in anemic subjects by transfusion of blood from patients with essential hypertension are very small and are no greater than those produced by transfusion of an equal volume of normal blood. This result is opposed to the idea that the raised blood pressure in essential hypertension is due to excess of pressor or deficit in a depressor substance in the circulating blood.

E. A.

Pickering, G. W., Kissin, M., and Rothschild, P.: The Relationship of the Carotid Sinus Mechanism to Persistent High Blood Pressure in Man. *Clin. Science* 2: 193, 1936.

The idea that certain forms of human hypertension might be due to an interference with the carotid sinus and depressor reflexes arose from the demonstration that high blood pressure could be produced in the experimental animal by denervating

the carotid sinus and arch of the aorta. A comparison of the chief features exhibited by patients suffering from the common forms of persistent hypertension with those exhibited by the animal with this form of experimental hypertension is instructive, for it reveals differences that are so striking as to leave no doubt as to the essentially different origin of human and experimental hypertension. Thus tachycardia is invariable in the experimental hypertension and exceptional in human hypertension; compression of the carotid artery below the sinus gives no response in the animal and a definite response in man; sensory stimuli produce a fall of blood pressure in the animal and a rise in man; in sleep the blood pressure falls to normal in the animal and remains elevated in man; and last, characteristic histological changes in the arterioles are absent in the experimental and usually present in the human form. It is not to be denied that there may be examples of hypertension in man which are similar in origin to the experimental form. Such cases must be uncommon and the authors are not satisfied that the evidence for their existence is adequate.

The function of the carotid sinus mechanism was tested in four groups of human subjects: (1) young adults with normal blood pressure, (2) elderly subjects with normal blood pressure, (3) patients with chronic nephritis and hypertension, (4) patients with essential hypertension. The differences in the response to carotid sinus compression shown by the various groups seemed to be entirely accounted for by differences in the initial levels of blood pressure and by differences in the degree of sclerosis of the large arteries. Digital obliteration of one carotid artery below the sinus produced, in all subjects with normal and high blood pressure, rises of blood pressure and pulse rate that were greater than those produced by control pressures on the neck and femoral artery.

E. A.

Pickering, G. W., and Kissin, M.: *The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension.* Clin. Science 2: 201, 1936.

No evidence was found that patients with chronic nephritic hypertension are abnormally sensitive to adrenalin. Evidence was presented against the view that essential and nephritic hypertension are due to hyperadrenalinemia. The suggestion that a relatively large rise of blood pressure in response to a cold stimulus is peculiar to potential or developed cases of essential hypertension is unconfirmed; however the series is too small to exclude the possibility that the rise of blood pressure is, in general, greater in subjects with hypertension than in those of similar age with normal blood pressures.

E. A.

Veal, J. Ross: *Vascular Changes in Intermittent Claudication. With a Note on the Value of Arteriography in This Symptom Complex.* Am. J. M. Sc. 192: 113, 1936.

The theories of the origin of pain in intermittent claudication are briefly reviewed.

An arteriographic study of 15 carefully selected cases of intermittent claudication is reported.

Attention is called to the fact that in 3 cases of undetermined etiology the radiographic evidence shows an entirely different type of lesion from that noted in the other twelve cases, in which the etiology was arteriosclerotic.

Arteriographic evidence is adduced to support the contention that the pain in intermittent claudication is not due to arterial spasm.



Hickman, J., Livingstone, H., and Davies, M. E.: Surgical and Anesthetic Risk in Cardiac Disease. *Arch. Surg.* 31: 917, 1935.

Since there were only six deaths due to cardiac disease and two deaths due to pulmonary disease related to the surgical intervention and anesthesia in 336 patients who underwent 345 operations, the resulting mortality of 2 per cent indicates that as a group patients with cardiac disease are fairly good surgical risks.

Angina pectoris, coronary occlusion, decompensation, hypertension and thyrotoxic heart disease are, in the order named, the most serious diseases with which one has to deal.

Contrary to the belief of several authors, inhalation anesthesia, particularly ethylene-oxygen anesthesia, is safe when a high percentage of oxygen is used and asphyxia or struggling is avoided. Ethylene-oxygen and local anesthesia have given the most satisfactory results in this series of cases. The use of spinal, ether or nitrous oxide-oxygen anesthesia has increased the incidence of postoperative complications and death.

AUTHOR.

Shipley, Arthur M., and Winslow, Nathan: Purulent Pericarditis. *Arch. Surg.* 31: 375, 1935.

Purulent pericarditis is an abscess and, like a collection of pus anywhere else, should be treated by incision and adequate drainage. Too much cannot be said in favor of early operation, but it should be remembered that late operation does not rob the patient of the hope of cure. Operative treatment should yield a cure in 50 per cent of the cases.

The best approach is the costoxiphoid route with resection of the left seventh, sixth, and fifth costal cartilages together with a portion of the sternum, when more room is needed. Therapeutic aspiration may be used, on occasion, with profit, but it has no curative value.

There are three chief factors that govern prognosis: (1) the time of the operation; (2) the type of the organism; and (3) the original condition of which the pyopericardium is a complication. Purulent foci elsewhere, unless detected early and promptly remedied, render the prognosis less favorable.

In the past seven years there has been no appreciable improvement in the operative mortality rate. Pyopericardium is a disease of youth. Eighty-three per cent of the patients are under thirty years of age. Seventy per cent of the patients have been males, and 30 per cent have been females. Troublesome postoperative adhesive pericarditis does not occur as often as it is generally supposed.

AUTHOR.

Winslow, Nathan, and Walker, W. Wallace: End-to-End Vascular Anastomosis: An Experimental Study. *Ann. Surg.* 103: 959, 1936.

After exposing the vessel, the circulation is arrested by bulldog clamps. The adventitia is grasped between a finger and thumb, drawn tight and cut off at a level with the rest of the vessel. Blood is gently stripped out of the lumen of the vessel, which is kept moist by washing with normal saline solution. The wall of the divided vessel is grasped near its open end with a fine smooth-mouthed pick-up forceps and four sutures of fine silk inserted through the margin of the divided vessel at equidistant points. These sutures are tied to the edge of the vessel with a single knot, and their free ends passed through the ring of bone. The ring is slipped over the vessel and a sufficient length of the vessel allowed to

protrude to cover the bone. The bone is held firmly in place by a barbed holder slipped between it and the end of the vessel to be cuffed. The redundant end of the stump is then rolled back over the bone by gentle traction upon the guy or stay sutures. The end of the distal stump is now slid over the segment of vessel which houses the ring of bone and, together with the cuff, is held securely in place on the bone by a temporary encircling ligature. At this stage of operation, the circulation is reestablished by removing the bulldog clamps. The holder is also removed. A ligature of fine silk is then introduced through each of the four holes in the ring and passed through the two ends of the divided vessel. These ligatures are anchored to the free margin of the ring of bone, after which the encircling ligature is removed and the guy sutures cut away.

By this technic the authors have had vessels with open lumina nearly a year after being anastomosed.

E. A.

Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: A Warning, With a Report of Two Deaths. J. A. M. A. 106: 1151, 1936.

Two deaths occurred following the intramuscular administration of digitalis and the intravenous injection of calcium gluconate chloride.

The manufacturers of calcium gluconate or chloride should preface their literature with a warning relative to the additive effect of calcium and digitalis when given simultaneously.

AUTHOR.

Wilson, H., and Roome, N. W.: Passive Vascular Exercise: Observations on Its Value in the Treatment of Peripheral Vascular Disease. J. A. M. A. 106: 1885, 1936.

As a result of treating twenty-three individuals with varying amounts of passive vascular exercise in the pavaex apparatus, the authors found little improvement definitely attributable to the specific therapy.

Twelve arteriosclerosis patients were given from 17 to 111 hours; five were slightly benefited; the rest showed no change. Only two of the eight patients with thromboangiitis obliterans were definitely benefited. One of three patients with major embolisms recovered, the authors being doubtful that the pavaex treatments affected the outcome one way or the other.

L. H. H.

## Book Review

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LE TONUS CARDIO-VASCULAIRE ET L'ÉPREUVE AMPHOTROPE SINO-CAROTIDIENNE. By D. Daniélopou, Paris, 1935, Masson et Cie., 200 pp. and 78 figures.

Since the mechanism of the carotid sinus reflex was worked out by Hering in 1927 and further elaborated by Heymans and his associates (1929), the literature has abounded in contributions to the mechanism of the working of the carotid sinus. To the literature of this subject Daniélopou and his associates have made many recent contributions. The volume which Daniélopou has now written brings together the views of this group of investigators about the functions of the carotid sinus. These views are at times at variance with those of other contributors to this subject, but it appears most frequently to be a question of interpretation, for the experimental observations are recorded and their deductions made; the data which have been reported by others are reinterpreted to bring them into line with their own notion of the "amphotropic" nature of the carotid sinus. The reader, however, is free to draw his own conclusions.

The book is very well planned. The historical section is well done. Then follows a discussion of the "mechanism of the cardio-vascular tone," then a description of techniques the author and his associates used (electrocardiograms and blood pressure measurements) followed in turn by an exposition of the amphotropic nature of the carotid sinus in the normal subjects and then, in turn, by its application to pathological situations, closing with a summary. It is surprising that no mention is made of Bronk's contributions to the physiology of the carotid sinus.

Naturally the clinician turns with interest to the section dealing with pathological situations. I think it is here that one finds the greatest difficulty in agreeing with the author, for he has found it too easy to explain phenomena of disease by calling into play the carotid sinus mechanism: changes interpreted as associated with valvular lesions, with myocardial disease, with emphysema, with angina pectoris; the mechanism of arterial hypertension (essential), of paroxysmal hypertension, of the cardiac irregularities, of pulsus alternans, all are brought into line with the working of the carotid sinus.

Those interested in cardiac physiology and disease will find this monograph suggestive and stimulating.

H. J. S.

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## Original Communications

### THOROTRAST ARTERIOGRAPHY OF THE EXTREMITIES WITH REPORT OF ILLUSTRATIVE AND UNUSUAL CASES\*

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WASHINGTON, D.C.

WITH the use of stabilized thorium dioxide sol, arteriography has become a practical and apparently harmless diagnostic procedure and a valuable method for studying the circulation in the extremities. Although arteriography has been practiced in a small way for many years, it has been less than ten years since it began to gain popularity. Thorotrast has been employed by those who have had the greatest experience with this procedure. Abroad, those who have practiced the method in the extremities most extensively are dos Santos and his co-workers,<sup>1, 2</sup> Heuser<sup>3</sup> and Fricke and his associates, including Leriche.<sup>4, 5</sup> In this country the main workers in this field are Allen and Camp,<sup>6</sup> Veal and McFetridge,<sup>7</sup> Horton,<sup>8</sup> and Barker.<sup>9</sup> Besides being used for demonstrating roentgenographically the arteries of the extremities, thorotrast is used similarly by some for making arteriograms of the cerebral vessels and of the abdominal aorta. Edwards<sup>11</sup> and Allen<sup>10</sup> have reviewed the earlier work concerning arteriography. The veins are also well demonstrated by direct injection cephalad into the venous channels.

Thorotrast,† a stabilized 25 per cent (by volume) colloidal solution of thorium dioxide, was first used in man in 1929 by Paul Radt,<sup>12</sup> formerly of Berlin, for demonstrating radiologically the liver and spleen. Thorium dioxide, being radiopaque and of high molecular weight, is rapidly removed from the blood stream and engulfed by the reticulo-endothelial cells of the body, and, where these are most concentrated, casts a shadow on the x-ray plate. As much as 75 c.c. is used for hepatosplenography. Because of a small degree of radioactivity, very

\*From the Georgetown University School of Medicine and the Gallinger Municipal Hospital.

Read before the American Heart Association, Section for the Study of Peripheral Circulation, at Kansas City, Mo., May 12, 1936.

†Manufactured by the Heyden Chemical Corporation of New York.

slow elimination and possible latent increase in the degree of radioactivity, the Council on Pharmacy and Chemistry of the American Medical Association has not accepted thorotrast as an approved chemical for use in man. Unfortunately, Radt, who has had the longest experience with it, has left Berlin and has lost access to his records and the follow-up of his patients. However, Rigler and his coworkers,<sup>13</sup> in employing thorotrast for hepatosplenography in 175 patients over a period of three and a half years, did not observe immediate or remote ill effects. Yater, Otell, and Hussey,<sup>14</sup> using this preparation in total doses of 75 c.c. for the same purpose in more than 200 patients over a period of nearly five years, have likewise not observed harmful effects.

The amount of thorotrast used for arteriography is much less than that used for hepatosplenography, unless several examinations are made, and any possible danger is therefore considerably lessened. For the upper extremity 5 to 12 c.c. (average 8 c.c.) are usually sufficient to produce good films. For the lower extremity 10 to 12 c.c. are commonly employed. Those who have practiced arteriography most have not noted ill effects. It is fair to mention, however, that several French authors have reported injury attributed to the procedure.

Because thorotrast when injected into the blood stream rapidly leaves the vascular system, films must be taken almost immediately to demonstrate the arterial tree, whereas for hepatosplenography the films may be made any time after several hours following the last injection.

#### TECHNIC OF ARTERIOGRAPHY OF THE EXTREMITIES

A routine technic has been used in our institution which for practical purposes gives satisfaction. Two films are usually sufficient for the upper extremity, two or three films for the lower extremity. In the upper extremity the injection is made through the skin into the brachial artery in the antecubital space just medial to the lacertus fibrosus, the needle pointing toward the axilla. In the lower extremity the injection is made through the skin into the common femoral artery 2 to 3 inches below the inguinal ligament, with the needle pointing toward the pelvis. The first two fingers of the left hand palpate the artery proximal to the point of injection and hold it in position. The needle, with the bevel up, is slowly inserted into the lumen of the artery for 1 to 2 cm. as nearly parallel with the artery as possible. When the needle is within the lumen of the artery, bright red blood spurts into the syringe with each beat of the heart, forcing the piston steadily outward. When this happens, the vessels well above the needle are occluded, and the thorotrast is injected with moderate rapidity but not hastily. If the injection requires more than moderate pressure or is attended with pain the needle is either plugged by a clot or a piece of tissue, or is not in proper position but is either in the wall of the artery or in the surrounding tissues. The occlusion of the needle should then be removed and the needle reinserted. After some experience the procedure is fairly simple. However, if there is much difficulty encountered in puncturing the artery because of deep position of the vessel, excessive fat, subcutaneous hemorrhage or edema, or spasm of the artery, it is perhaps wiser to desist or at least to postpone the attempt. An 18 gauge, 2 inch long, preferably new needle is most useful for the injection. Arteriography, of course, must be performed aseptically.

To prevent spasm of the punctured artery and to relieve the patient's apprehension, I regularly inject intravenously 1 ampule of spasmalgin\* about fifteen minutes before the procedure.

The patient lies supine on the x-ray table, and the x-ray plate is placed under the extremity to be studied. Films measuring 14 by 17 inches are used except for the foot alone. Two exposures are made on each film, one-half of the film being covered by a lead shield while the other half covered by the limb is being exposed. After the region of the extremity to be used for injection is prepared and draped with sterile towels, the skin and tissues around the artery are anesthetized with a local anesthetic, such as 1 per cent novocaine. When the arm is to be filmed, a sphygmomanometer cuff previously applied is pumped up above the systolic pressure after the artery has been punctured. Approximately 8 c.c. of thorotrast (which is marketed in ampules of 12 c.c. and 25 c.c.) is then injected, the thorotrast being at room temperature and undiluted. As soon as the injection is completed, the needle is withdrawn, and pressure with an alcohol sponge made at the point of injection to prevent leakage of blood from the artery. The forearm and hand, palm upward and digits slightly separated, are rapidly posed on the plate. The first exposure is then made. The arm and hand are next shifted to the other half of the film and posed, and the lead shield is placed on the exposed half. The sphygmomanometer cuff is then rapidly deflated and four beats allowed to pass into the forearm, when the second exposure is made. These two films usually show the arteries of the forearm well filled. In the first film usually the palmar arch is also shown, and in the second film some of the digital arteries are frequently demonstrable. In the latter film some of the veins are also often filled.

When the lower extremity is to be filmed, half of the plate is placed so that the lower two-thirds of the thigh and the upper fourth of the leg in the anteroposterior position is on half of the film. After the injection of approximately 12 c.c. of thorotrast has been made into the femoral artery, an assistant gently occludes the artery against the pubic bone with his fingers. The first exposure is then made. With the artery still occluded, the plate is shifted downward so that the rest of the extremity, either in the anteroposterior position or slightly flexed in the lateral position, is on the unexposed portion of the film. The fingers of the assistant are removed from the artery for five heartbeats and reapplied, the second exposure then being made. If a third film showing the foot placed sole downward is desired, the leg is flexed at the hip and knee and the foot is posed on a smaller plate. The assistant then removes his fingers, and the exposure is made. The first film shows the large arteries of the thigh and the branching of the popliteal artery. The second film shows the main arteries of the leg and foot. The third film often shows the main arteries of the foot but rarely much of the digital branches.

The following x-ray technic is employed: Tube distance 30 inches, 0.5 mm. aluminum filter, high speed screens, 100 milliamperes,  $\frac{2}{10}$  second, voltage varied according to thickness of the part (3 cm., 46 K.V.P.; 4 cm., 47 K.V.P.; 5 cm., 49 K.V.P.; 6 cm., 52 K.V.P.; 7 cm., 55 K.V.P.; 8 cm., 57 K.V.P.; 9 cm., 59 K.V.P.; 10 cm., 62 K.V.P.; 11 cm., 65 K.V.P.; 12 cm., 68 K.V.P.; 13 cm., 71 K.V.P.; 14 cm., 74 K.V.P.; 15 cm., 76 K.V.P.).

This technic, after some experience, usually gives all of the information desired. It can be used in any hospital without special equipment. A more ideal method is that of Caldas<sup>15</sup> with his radio carousel, a costly apparatus which permits six exposures of the same part to be made at intervals of one second after the injection of the contrast medium. This method, while ideal in many respects, is not absolutely necessary, but it gives more exact information as to the rate of circulation in the extremity, and it obviates the necessity of timing.

\*Spasmalgin, prepared by Hoffmann-LaRoche, Inc., contains in each ampule of 1 c.c., papaverine hydrochloride 0.02 gm. ( $\frac{1}{2}$  grain), pantopon 0.01 gm. ( $\frac{1}{2}$  grain), and atrinal (atropine sulphuric acid ester) 0.001 gm. ( $\frac{1}{100}$  grain).

## CAUTIONS IN INTERPRETATION

Great caution must be observed in interpreting films in which there is incomplete filling of the vessels. If there is doubt as regards the possibility of obstruction, the arteriograms should be made again and a little more time given for the contrast medium to fill the arteries in question. Normally it takes "from six to nine seconds for the column of thorotrast, after it enters the blood stream, to pass from the femoral triangle down to the vessels of the foot, the return flow, naturally, being slower" (Veal and McFetridge). Vascular disease, of course, causes variations in the rate of progression of the column, as does also any increase or decrease in the rate of the systemic circulation.

Filling of the digital vessels of the hand and even more so of the foot is the most uncertain feature of the procedure. Even in normal limbs when several of the digital arteries are filled, the others may not be. Fortunately, most of the data usually desired concern the larger vessels of the extremity.

## REACTIONS

Systemic reactions of any consequence due to the injection of thorotrast are rarely encountered. However, if some of the medium is injected into the tissues about the artery there is usually severe local pain with some local swelling and heat. In hypersensitive individuals the pain may be felt in the whole extremity. Hot moist compresses and analgesic drugs give considerable relief, and the effects subside in from two to four days. Even if the thorotrast is injected into the wall of the artery, no serious damage is done.

## THE NORMAL ARTERIOGRAM AND THE COLLATERAL CIRCULATION

A knowledge of the normal arteriogram is essential in interpreting abnormal states. This may be obtained by dissection of cadavers and amputated extremities, by the study of arteriograms of normal extremities, and by the study of arteriograms of the injected cadaver or of amputated limbs. Although there are many variations of the normal vascular tree of the extremities, the main arteries usually conform to a standard pattern.

Radiograms of normal limbs of cadavers injected with a radiopaque substance show a voluminous vascular tree; whereas, arteriograms of living subjects with normal extremities show relatively few vessels, mainly the larger ones and comparatively few of their cutaneous, muscular, osseous and anastomotic branches, especially in the lower extremity. The former is explained by the fact that there is no circulation in dead limbs and all vessels washed out and refilled with the contrast medium are demonstrated. In the resting extremity of the normal living subject, however, only those vessels contain the thorotrast which

are just sufficient to nourish the tissues in a state of relative inactivity. Furthermore, owing to the circulation of blood and a lag in the diffusion of the thorotrast, only a certain number of vessels are made visible at

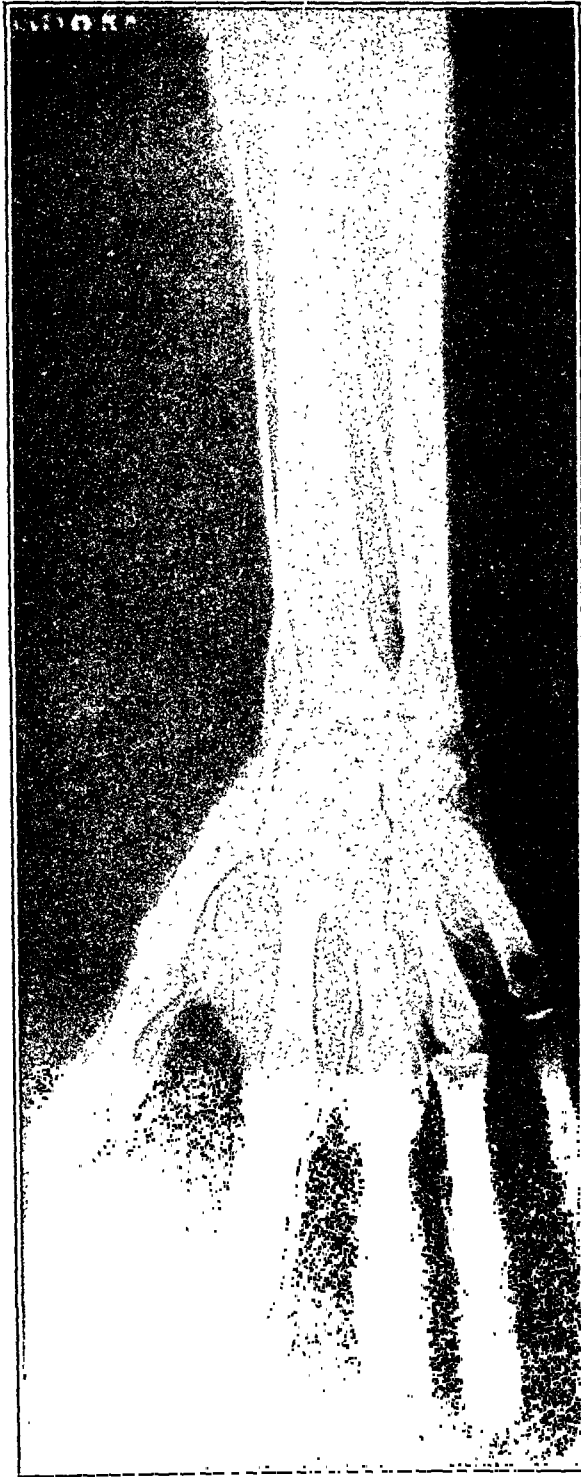


Fig. 1.—Normal arteriogram of forearm and hand.

any one instant. If arteriograms could be made while the subject were running, undoubtedly a great many more vessels would be seen to contain the contrast medium since the muscular branches would be functioning more effectively and the diffusion would be more rapid.



The normal arteriogram shows the arteries to be smooth walled, relatively direct in their course, and very gradually tapering down to the smallest branches (Fig. 1). When visible, the veins are seen to be of greater lumen, not so opaque, and much more wavy, tortuous and interlacing. The sites of the valves in the larger veins are often discernible, due mainly to localized bulging just above them.

When there is obstruction of an artery from any cause, the so-called collateral circulation becomes apparent. The head of pressure being the same as before the obstruction took place, more blood is forced down the branches arising from the occluded vessel proximal to the point of occlusion. The number of collateral vessels made visible depends upon the degree of involvement of the branches of the obstructed artery or arteries, the rapidity of the occlusion, and the state of the general circulation. Allen<sup>16</sup> and others are probably correct in assuming that most, if not all, of the so-called collateral vessels are vessels which previously existed, since a comparison with the radiograms of the injected normal limbs of cadavers shows in general the same vessels, since the collateral vessels are demonstrable relatively soon after the occlusion occurs, and since the main collateral vessels are relatively large and lengthy. However, it is quite possible that new anastomoses may develop in time since vessels are seen in cases of gradual occlusion passing from the artery above the area of occlusion or from another vessel to join the occluded vessel below the area of occlusion and thus bridging the gap (Fig. 2). Most of the collateral vessels are either normal anastomotic branches or muscular branches. In time they become larger in diameter of lumen, stretched and elongated, and often tortuous and resembling a corkscrew. Many of their smaller branches may arise more or less at a right angle. Many more small and apparently interlacing vessels are also demonstrable in the arteriograms after occlusion of an artery.

The fact that the normal arteriogram shows relatively few vessels and mainly the larger and more direct ones probably explains why it is usually the larger arteries that are most affected by degeneration. These are the vessels bearing the brunt of the circulatory load, and the factor of strain is important in the localization of degenerative processes. The smaller, less constantly used vessels are frequently less severely affected and are able therefore in many cases to come to the aid of the damaged limb and to take over part or all of the function of the affected vessel.

#### ARTERIOSCLEROTIC GANGRENE AND SELECTION OF THE SITE OF AMPUTATION

Although arteriography is of interest and probably of value in studying the pathologic-physiologic disturbances of the circulation in the extremities, undoubtedly its greatest practical value lies in its use for helping to determine the best site for amputation of the lower extremity in cases of arteriosclerotic gangrene. Veal and McFetridge<sup>7</sup> have

stressed the value of arteriography for this purpose. However, it by no means dispenses with the other forms of clinical examination.

Arteriosclerosis is manifested by irregularity in the wall of the artery and narrowing or obliteration of the lumen at intervals. The larger

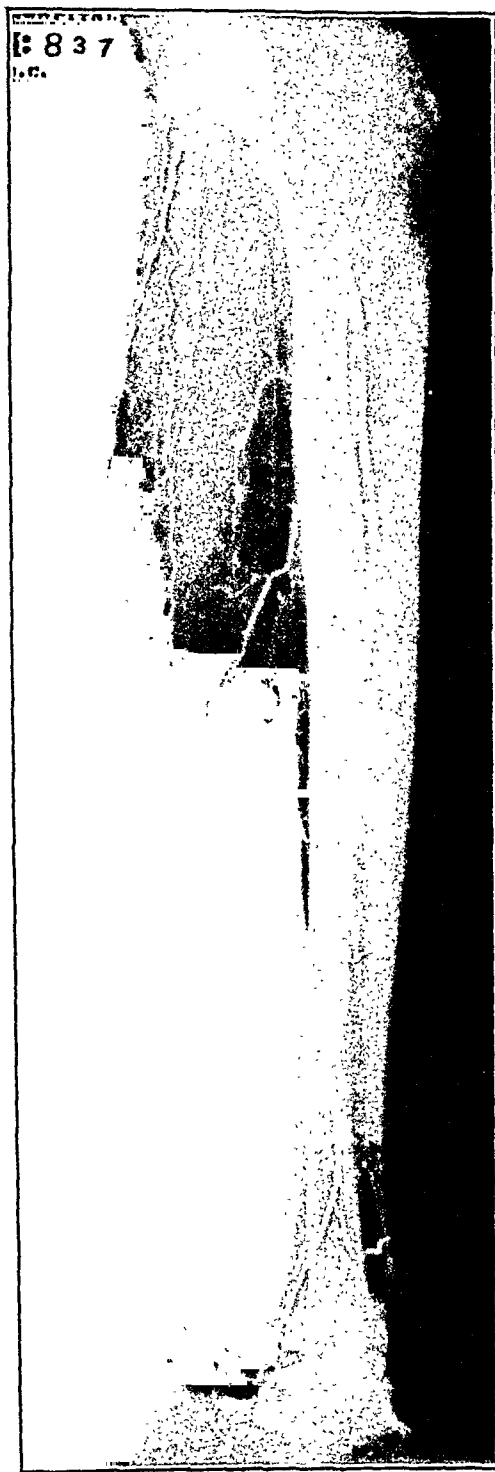


Fig. 2.—Arteriosclerosis obliterans. Anterior tibial artery interrupted in lower half, posterior tibial in upper half. Small collateral arteries bridging across the gaps. Collateral arteries numerous in the calf.

arteries are often wavy instead of straight. Small branches may end abruptly. This process affects mainly the larger arteries but often also the medium-sized and even the small ones. In uncomplicated arterio-

sclerosis the number of smaller arteries, or collaterals, is often moderately or greatly increased, depending upon the degree of involvement of the larger arteries and the relatively mild or moderate involvement of the muscular and other branches. In other words, the greater the involvement of the large arteries and the less the involvement of the smaller arteries, the more extensive the collateral circulation will be.

Although gangrene may be due to simple diminution in caliber of the lumen, it is more often due to thrombosis of one of the larger



Fig. 3.—Arteriosclerosis obliterans. Occlusion of posterior tibial artery. Gangrene of foot.

degenerated arteries. When the gangrene is due to simple occlusion of the lumen by the arterial degeneration, usually only a toe or two is affected, whereas, when there is more extensive gangrene, thrombosis and occasionally embolism may be assumed to exist. The thrombus usually extends well above the upper limit of gangrene.

For instance, a diabetic patient aged seventy-two years developed gangrene of the toes of the left foot. The arteriogram (Fig. 3) showed complete occlusion of the posterior tibial artery about 5 cm. below its origin, as well as severe arterio-

sclerosis of the other arteries. Amputation was performed in the middle of the thigh, but even then there was some sloughing of the stump, requiring a secondary operation.

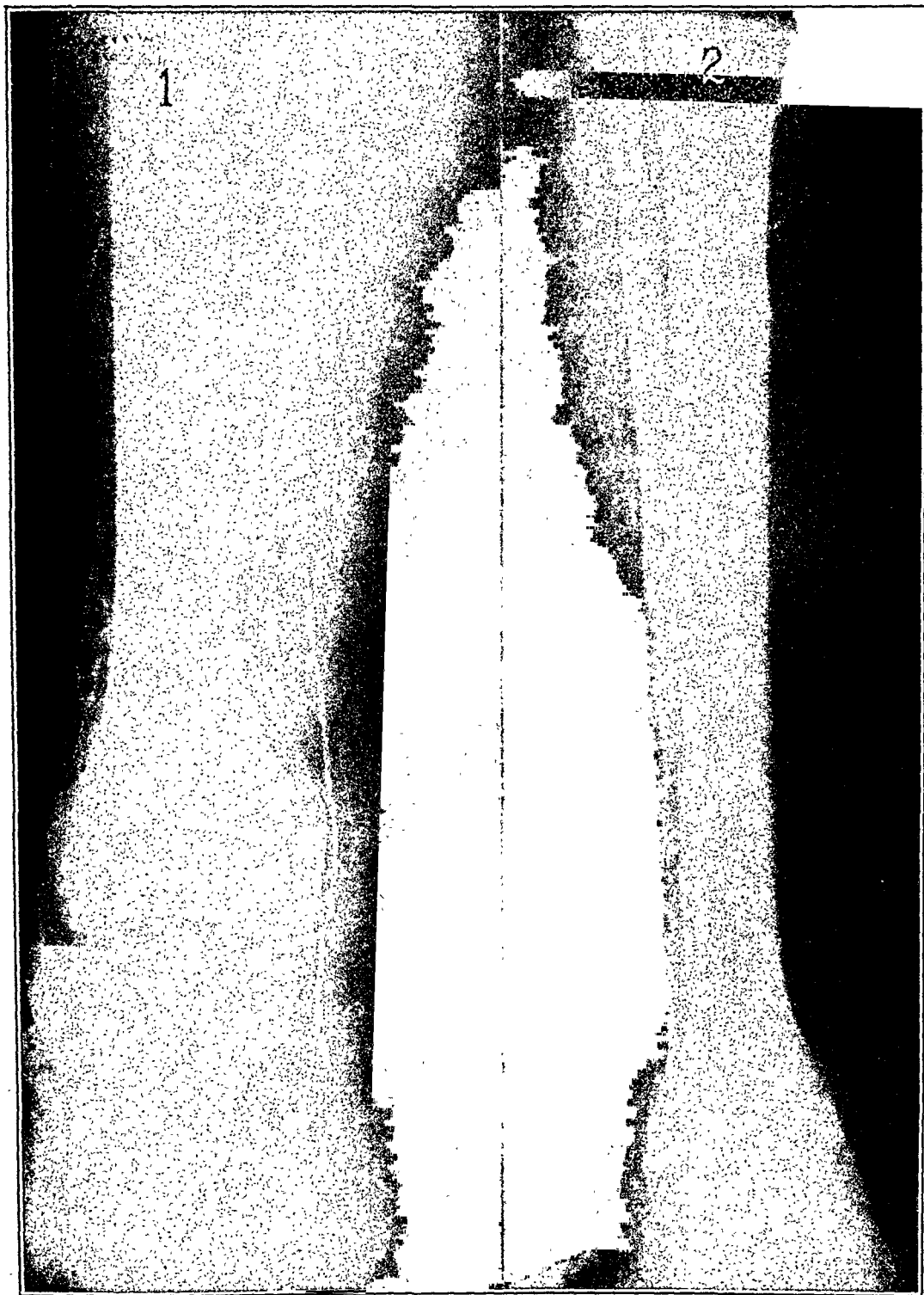


Fig. 4.—Thromboarteriosclerosis obliterans. Complete occlusion of popliteal artery by a thrombus. Large, dry ulcer on heel. Practically no arteries visible below calf.

Another diabetic, aged fifty-seven years, developed an indolent shallow ulcer on the heel of the right foot with edema of both legs. Although thermographic and oscillometric studies revealed that the occlusion was above the knee, the arterio-

gram (Fig. 4) showed definitely that there was complete occlusion in the upper portion of the popliteal artery with relatively little collateral circulation even after two months. Amputation was performed in the lower third of the thigh. Dissection and study of the vessels showed an old thrombus beginning 3.5 cm. below the site of amputation, extending for 10.5 cm. and ending 2.5 cm. above the origin of the anterior tibial artery. All of the larger arteries were markedly arteriosclerotic and calcified. There were other thrombi and sites of simple occlusion in the main branches of the popliteal artery. Most of the veins were also thrombosed. Healing was uneventful.

In still another patient, a negress, aged forty-five years, with advanced carcinoma of the uterus, a severe pain had suddenly developed in the calf of the right leg two weeks before admission to the hospital. The pain continued, and the

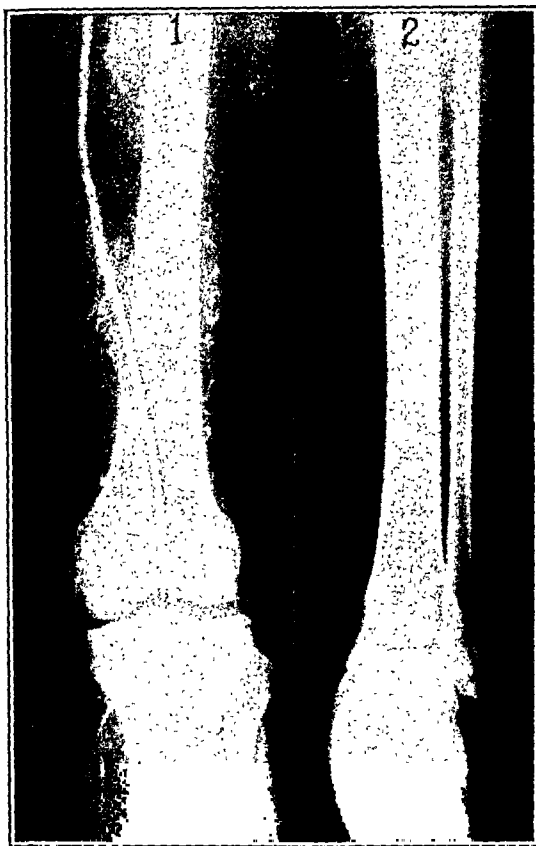


Fig. 5.—Embolie occlusion of popliteal artery. Gangrene of foot and lower third of leg. Very few collateral arteries visible below knee.

leg began to swell. The foot became cold and insensitive. The whole foot and lower third of the leg were found to be cold, smooth and dry, and the toes were becoming shriveled. Pulsations in the dorsalis pedis and posterior tibial arteries could not be felt, but it was thought that pulsation could be obtained in the popliteal artery. However, an arteriogram showed abrupt occlusion of the popliteal artery (Fig. 5) just above the knee joint, and relatively little collateral circulation below the knee. Amputation was performed at the knee joint. Dissection and study of the vessels of the amputated limb showed a gray thrombus, apparently an embolus, in the popliteal artery beginning 8 cm. below the site of amputation and extending far down into the two tibial and the peroneal arteries. There was moderately severe atherosclerosis. The veins were distended and filled with relatively fresh thrombi. Healing was complicated by secondary infection of the stump.

## THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

Arteriography in cases of thromboangiitis obliterans, while of questionable practical value, is nevertheless of great importance in the study of the pathogenesis of the disease. It shows definitely that the disease

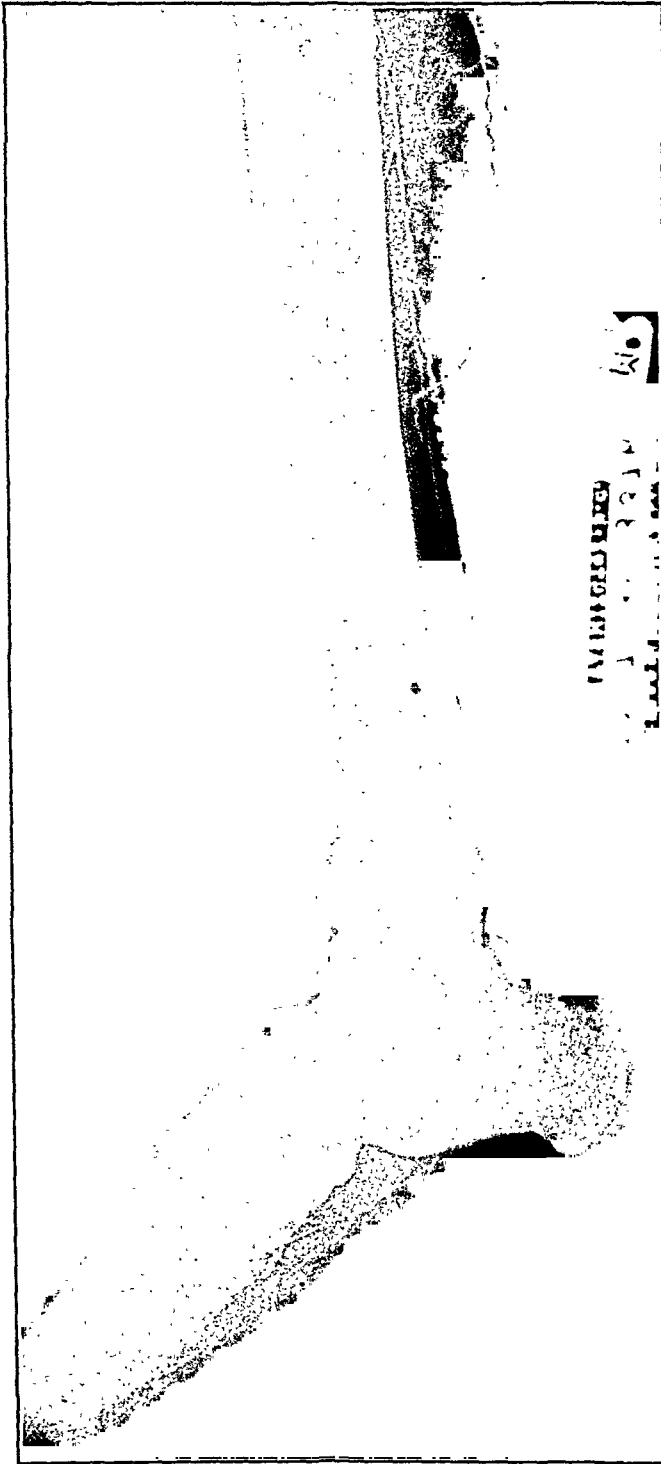


Fig. 6.—Thromboangiitis obliterans. Main vessels almost entirely occluded. Long, wavy collateral arteries nourishing leg. Lesions healed.

frequently involves all four extremities. It shows also that it is a polyphasic disease, i.e., various stages of the disease may be present in various arteries and branches in the same limb. The collateral circulation is the most extensive of all vascular diseases, but even the

collaterals may become involved. Brief accounts of a few cases will serve to illustrate some of the main characteristics of the disease.

In the case of an Irishman, aged thirty-two years, who had had manifestations of Buerger's disease of the legs for only a year, gangrene of the left foot pro-

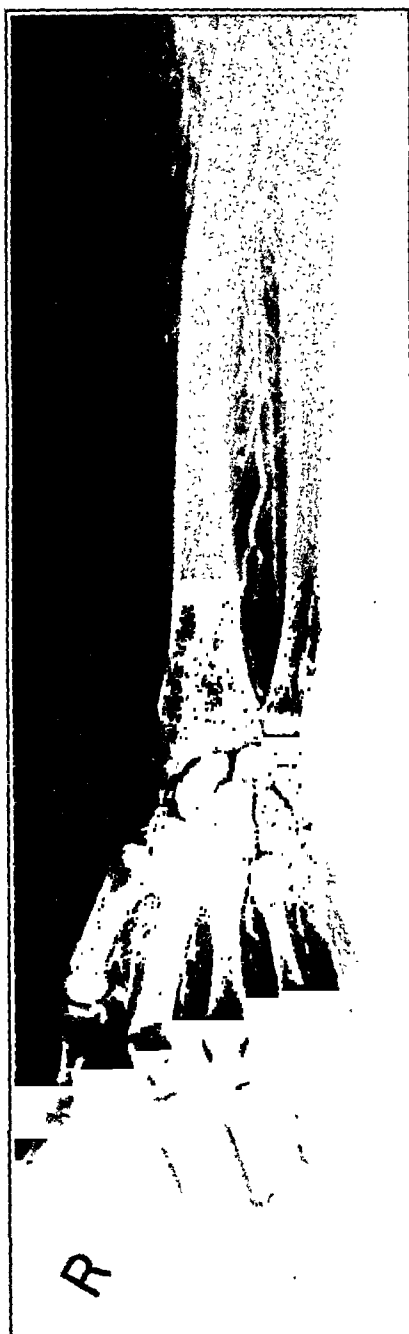


Fig. 7.—Thromboangilitis obliterans. Radial and ulnar arteries practically completely occluded. Small collateral arteries and extension of interosseous supply hand. No trophic changes in hand.

gressed rapidly during a severe attack of pharyngeal diphtheria, while the pre-gangrenous condition of the right foot improved. Amputation was performed above the left knee, followed by fairly rapid healing of the stump. Although the right foot at the time showed very little trophic change, arteriograms revealed that

all of the large vessels below the knee were practically completely occluded and that the circulation was maintained by long wavy collateral arteries (Fig. 6). There was clinical evidence that the ulnar arteries might be involved, although the circulation in the hands appeared to be normal. Arteriograms of the left forearm and hand showed that the lower end of the ulnar artery from just above the wrist joint was obliterated, but a small collateral branch continued down from the upper end of the occluded portion and joined the palmar arch. The interosseous artery also sent branches down into the palm. The other arteries appeared to be normal. This patient later died of a cerebral abscess complicating a pulmonary abscess, and dissection and study of the vessels of the leg showed extensive involvement of all of the main arteries and some of the veins, including the femoral.

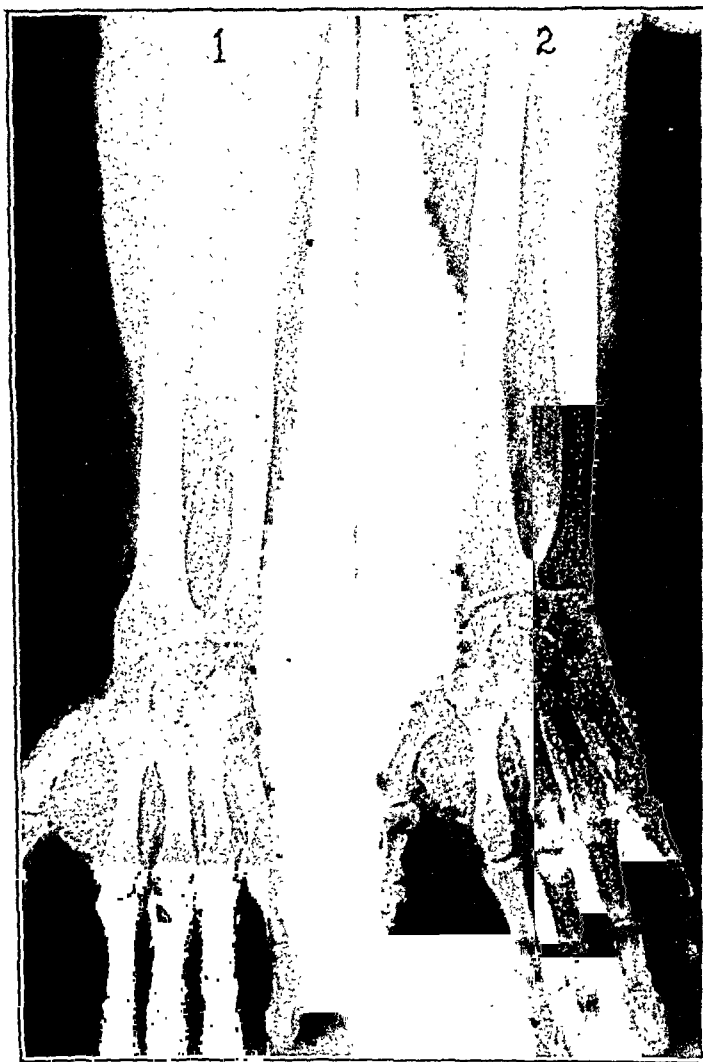


Fig. 8.—Thromboangiitis obliterans. Extensive and extreme involvement of radial, ulnar, and interosseous arteries. Many fine collaterals supply blood to forearm and hand. Tip of second finger had been lost and bed of thumb nail was infected.

Another Gentile, aged forty-seven years, who had had his right leg amputated above the knee eleven years before and who lately had been having severe pain in the left foot with evidence of impending gangrene, had absence of pulsation in the radial and ulnar arteries of both hands, although the circulation was quite adequate. Pulsations could be felt in both interosseous arteries. Arteriograms of the right forearm and hand showed both the radial and ulnar arteries to be completely occluded in their entire extent (Fig. 7). Long, twisting collateral arteries passed down into the hand and together with prolongation of branches of the interosseous artery maintained a good blood supply to the hand and fingers.



A Jew, aged thirty-eight years, had had a typical history of thromboangiitis obliterans for six years. Some toes had been lost by spontaneous and surgical amputation, and the distal phalanx of the right index finger had also amputated itself.



Fig. 9.—Thromboangiitis obliterans. Same case as Fig. 8. Popliteal and tibial arteries occluded. Main blood supply to leg and foot by way of sural branches. Gangrene of toes.

While he was in the hospital recently because of severe gangrene of both feet, precipitated by frost-bite, arteriograms were made of the arms and legs. The vessels of the left arm and hand were essentially normal, but the radial, ulnar,

and even the interosseous arteries of the right were almost completely occluded, and the circulation was maintained by a great number of thin, interlacing collaterals (Fig. 8). This is the first case I have seen with severe involvement of the interosseous artery from any cause. The arteriograms of the lower limbs presented essentially the same appearance. The popliteal artery and its main branches were completely occluded from just below the knee joint. Practically all of the blood supply to the leg and foot was obtained by extensions and ramifications of the sural arteries, the two large inferior muscular branches of the popliteal artery which are normally distributed to the gastrocnemius, soleus and plantaris muscles (Fig. 9).

An arteriogram of the arm and hand of a Gentile aged thirty-eight years, who eight years before had had lumbar sympathetic ganglionectomy and ramisectomy followed by remission of all pregangrenous manifestations, was normal; but during injection of the thorotrast into the brachial artery he suffered excruciating pain in the forearm and hand, followed by absence of arterial pulsations and blanching of the hand for several minutes.

This is the second case I have seen of severe arterial spasm due to arterial puncture in spite of the previous administration of papaverine. It indicated in this case that there was a large element of spasm associated with the thromboangiitis obliterans and explained the success of the ganglionectomy and ramisectomy. There was no question of the diagnosis of thromboangiitis obliterans, since attacks of superficial phlebitis had occurred and other evidences of the disease existed. Intravenous injection of a second ampule of spasmalgin quickly relieved the spasm, but pain at the site of injection continued for some time, apparently due to the injection of a small amount of thorotrast into the tissues. The other case of arterial spasm concerned a woman with Raynaud's disease, whose artery I tried to inject while she was having an attack.

#### ARTERIOVENOUS FISTULA

Both congenital and acquired arteriovenous fistulas are demonstrable by arteriography. Besides showing the exact site or sites of fistulas the arteriograms indicate the size of the fistula but not the extent of the collateral circulation. Horton and Ghormley<sup>17</sup> and Friehe and Lévy<sup>18</sup> have had experience with congenital fistulas. I have made arteriograms in four cases of the acquired form, one of which was reported in 1933 by Yater and White.<sup>19</sup>

Horton and Ghormley<sup>17</sup> have pointed out that in congenital arteriovenous fistula there are increased size and tortuosity of arteries leading to the fistula, "pooling of the medium in the region of the fistula, and absence of filling of the arteries distal to the fistula."

In acquired fistulas the appearance of the arteriograms is dependent mainly upon the size of the fistula and the size of the vessels involved. Usually the fistula involves a relatively large artery and vein, since it is most often produced by gunshot or stab wounds and the missile must pass through both the artery and vein without completely severing them. The small fistulas are usually due to buckshot.

When the fistula is small and single, the arteries both above and below the fistula may be seen in the arteriogram; when large, they are probably never seen, the reason being that in the latter practically all of the blood passes rapidly from the artery through the fistula into the veins. In a small fistula the veins distal to the fistula are not so large, numerous or tortuous as they are in the case of a large fistula. In either case there is a saccular enlargement of the vein in the region of the fistula, its size being dependent also on the size of the fistula and the size of the vessels involved. This is not a true aneurysmal sac, but merely a dynamic enlargement which collapses after death or removal at operation.

With large fistulas the veins distal to the communication assume the rôle of the arteries in nourishing the extremity. This arrangement might work satisfactorily if it were not for the difficulty in the return of venous blood from the part. As a matter of fact, just how it gets back to the veins proximal to the fistula is unknown, but the study of one of my cases suggested a mechanism.

A brief report of the four cases studied will demonstrate these features. A more detailed report of the cases will be published elsewhere.

The first case was that of a negro boy, aged fifteen years, who had been shot with buckshot, five months before, in the right arm. All of the physical signs of arteriovenous fistula were present in the antecubital fossa. The arteriogram showed a saccular enlargement in the first part of the ulnar vein. The arteries distal to the sac were fairly well filled, as was also the brachial vein proximal to it but not the veins distally. These findings and the fact that there was little change in the pulse rate and blood pressure when the fistula was closed indicated that the fistula was very small.

The second case concerned a negro, aged forty-four years, who had been shot with a shotgun in the right popliteal region twenty-eight years before. His complaint was not related to the arteriovenous fistula, typical evidences of which were found in the right lower extremity. Arteriograms showed great enlargement of the femoral and great saphenous veins proximal to the fistula, with a saccular bulging behind the knee. The popliteal artery was not visible above or below the knee, but few of the veins below the sac contained the contrast medium. Operation revealed a very small fistula, and the sac was not apparent in the specimen.

The third case was that of a white man, aged thirty-four years, who had symptoms suggestive of subacute bacterial endocarditis. He had received a gunshot wound of the left thigh twenty-six years before. Physical signs of an arteriovenous fistula were prominent in Scarpa's triangle. In making the arteriogram the femoral artery had necessarily to be punctured just proximal to the fistula. The artery leading to the fistula was not demonstrable in the film. The vein formed a large fusiform sac in the upper thigh; the veins distal to it were visible but not distended or tortuous; and the artery was not evident. The fistula was thought to be of relatively small size. Operation, performed with the hope that bacterial vegetations might be present in the fistula, showed it to be about 2 mm. in diameter. No vegetations were found, as in the case of Hammon and Rienhoff,<sup>20</sup> and ten days later necropsy revealed subacute bacterial endocarditis.

In the fourth case, a negro, aged fifty-two years, had been shot through the left knee with a 0.38 caliber rifle fourteen years before. The leg was very large, and the superficial veins were very prominent. A large chronic ulcer was present on the an-

terior surface between the knee and the ankle. Six arteriograms made serially after the injection of 50 c.c. of thorotrast (the large amount being given because of the great size of the veins) did not show any of the main arteries, but the great

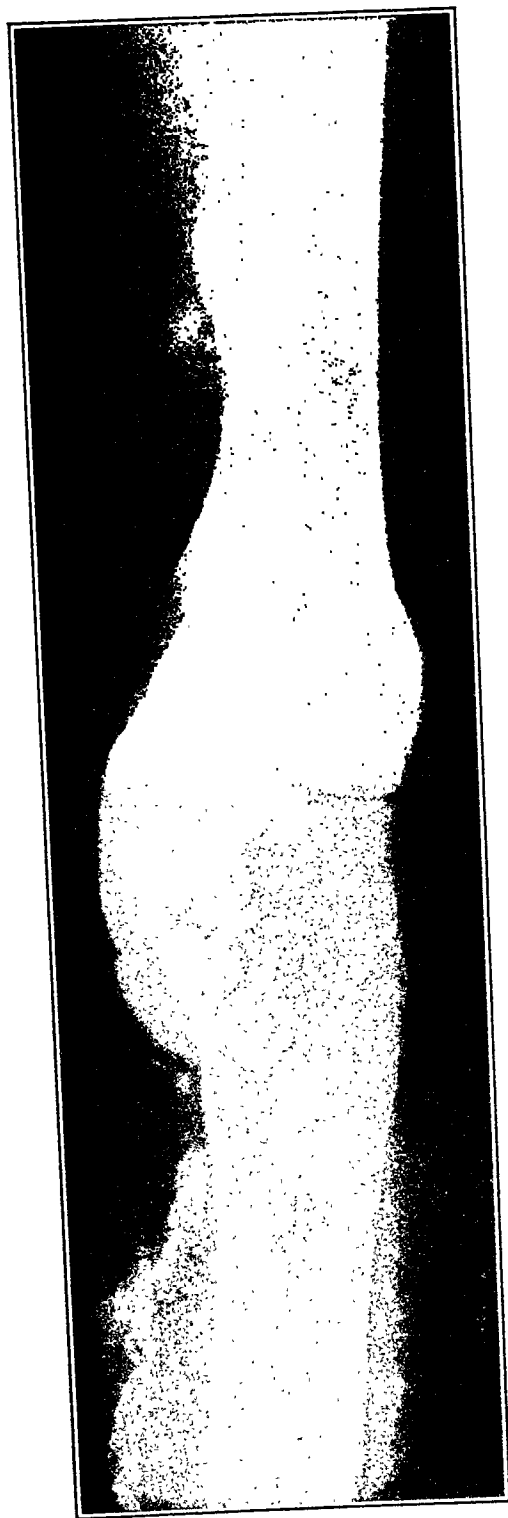


Fig. 10.—Large arteriovenous fistula between popliteal artery and vein. Film No. 2 of a series. Popliteal vein greatly dilated. Tributary veins numerous and tortuous. No arteries visible.

saphenous vein proximal to the fistula was well filled, and the popliteal vein was tremendously distended (Fig. 10). Subsequent films showed many very tortuous veins becoming visible below the fistula, while the saphenous and popliteal veins were not so distinct. In the last films, however, the distal veins became less distinct,

whereas the great saphenous and popliteal veins became visible again. These findings indicated that the fistula was a large one. They suggested also that the contrast medium went down the veins and came back the same way, there being apparently two simultaneous currents in the same vein.

#### ANEURYSM

Aneurysms are well demonstrated by arteriography, as shown by Friehe and Lévy.<sup>21</sup> Barker<sup>9</sup> has reported a case of spontaneous false aneurysm



Fig. 11.—Ruptured popliteal aneurysm. Popliteal artery interrupted, but tibial arteries visible. Pool of thorotrast in upper calf.

of the popliteal artery so demonstrated. My series includes a case of ruptured popliteal aneurysm.

The patient was a negro, aged forty-nine years, who six months before had been struck in the calf of the right leg by a falling tub. This incident had been followed by swelling in this region, and when examined the whole leg was found to be greatly enlarged, with a soft mass in the popliteal fossa. On one occasion the femoral artery was injected with thorotrast, on another, the femoral vein. The first films showed interruption of the popliteal artery for some distance, with a pool

of thorotrast in the upper part of the calf (Fig. 11). The second films showed the popliteal vein compressed on the peripheral side of the swelling containing this pool, thus accounting for the edema. Dissection of the leg following amputation above the knee showed a very large hematoma in the calf, which had formed as the result of rupture of a small popliteal aneurysm, probably syphilitic.

#### UNUSUAL CONDITIONS

*Arterial Spasm Due to Ergotamine Tartrate Resulting in Gangrene of the Feet.*—Arteriograms were made in the case of a white fisherman, aged sixty-four years, who was given large doses of gynergen hypodermically to relieve pruritus due to the jaundice of toxic hepatitis. Evidence of impairment of circulation in

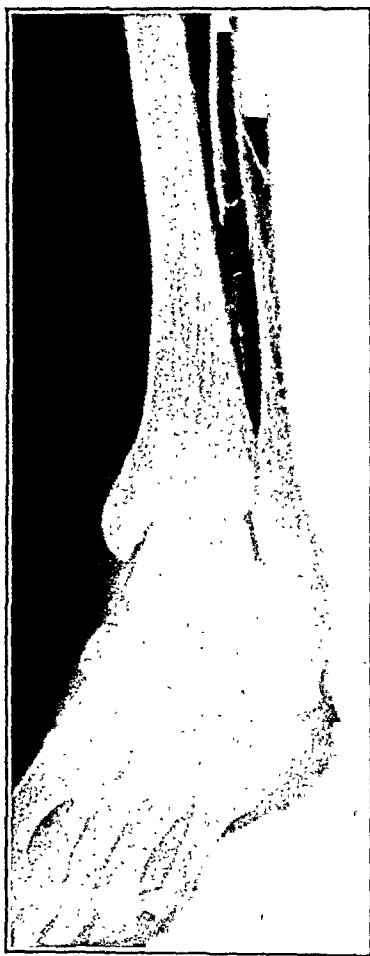


Fig. 12.—Spasm of tibial arteries due to overdosage of ergotamine tartrate. Occlusion in lower third of leg. Long collaterals to foot. Gangrene of distal halves of both feet.

both feet developed on the third day, and dry gangrene resulted after a few days. The arteriograms made more than a month later showed normal arterial shadows down to the lower third of the leg, where they faded out into a point (Fig. 12); long, thin collateral arteries passed downward to the foot from above the upper limits of occlusion. After amputation the arteries were found to be severely constricted and at intervals contained thrombi.

*Thromboangiitis Obliterans (?) in a Negro.*—A negro, aged forty-three years, had been having parts of the toes of both feet ulcerate and fall off for nine years. Pulsations were absent in both dorsalis pedis arteries and in the left posterior tibial artery. Arteriograms of the right leg showed the anterior tibial artery missing, the posterior tibial normal, and numerous collateral arteries in the leg and foot (Fig.

13). Arteriograms of the left leg showed obliteration of both tibial arteries in their lower third. A biopsy of the left dorsalis pedis artery revealed in microscopic sec-



Fig. 13.—Thromboangiitis obliterans (?) in a negro. Occlusion of anterior tibial artery. Gangrene of toes.

tions the lumen completely filled with old fibrous tissue containing a goodly number of small vessels. The media, which was moderately fibrotic, contained a number of new arterioles. The case suggests thromboangiitis obliterans, but that disease

has never been reported in the negro. On the other hand, syphilitic thromboarteritis is a possibility. The patient has been treated for syphilis, and although his Kahn test is negative, he has signs of early aortic regurgitation.



Fig. 14.—Thromboarteritic occlusion of femoral artery and branches. Many long collateral arteries. Gangrene of foot.

*Obliteration of All of the Large Arteries of One Lower Extremity.*—The most astonishing case is that of a negro, aged thirty-four years, who for three and a half months was suffering from ulceration and gangrene of the fourth and fifth toes of the left foot. He had had a penile lesion one year before, and his Kahn test of the



blood was four-plus. The right lower extremity was clinically normal, but the arteriograms showed evidence of an occlusive process of slight degree in the tibial arteries. The whole left foot was affected by dry gangrene, and there were no pulsations in the arteries of that limb below the femoral triangle. Arteriograms revealed complete absence of shadows of the femoral, popliteal and tibial arteries, but collateral arteries were abundant throughout the thigh and leg (Fig. 14). Amputation was performed below the knee because of the good collateral circulation. There was very little bleeding during the operation, and no large arteries had to be ligated. Some gangrene has occurred in the stump, but amputation has been too recent to permit an estimate of the ultimate outcome. Dissection of the amputated limb showed the tibial arteries to be small fibrous cords. Microscopic sections revealed obliteration of the lumina of the arteries with fibrous tissue and new vessels and vascular canals therein. There were also some deposits of hemosiderin. The media was relatively intact except for secondary changes and some new vessels. The etiology was not clear.

#### SUMMARY

Thorotrast, a stabilized solution of thorium dioxide, is in most respects an ideal medium for arteriography, and its use has made arteriography a practical and valuable procedure. It has been employed in many cases without apparent harm. The technic is relatively simple, and arterial puncture is not difficult after a little practice. Interpretation of the films requires some experience.

Type of vascular lesion, sites of occlusion, and extent of collateral circulation are readily demonstrable. Perhaps the most practical use for arteriography is to aid in selecting the best site for amputation when gangrene has supervened. However, arteriography does not supplant careful clinical investigation, such as physical examination, thermographic studies, oscillographic readings, and determination of the vasomotor index.

A simple routine method of arteriography has been described. Types of vascular lesions demonstrable by it have been discussed. Typical and unusual cases have been briefly reported and illustrated by photographs of arteriograms.

#### REFERENCES

1. dos Santos, R., Lamos, C., and Caldas, J. P.: *L'artériographie des membres*, Bull. et mém. Soc. nat. de chir. 58: 635, 1932.
2. dos Santos, R.: *L'artériographie en série*, Bull. et mém. Soc. nat. de chir. 59: 35, 1933.
3. Heuser, C.: *Radiografía de los arterias por medio de la inyección intravenosa*, Rev. méd. latino-am. 17: 1572, 1932.
4. Friel, P., and Lévy, A.: *Renseignements fournis par l'artériographie dans quelques affections vasculaires des membres*, Lyon chir. 31: 660, 1934.
5. Leriche, R.: *Sur la bénignité des artériographies au thorotrast*, Bull. et mém. Soc. nat. de chir. 61: 175, 1935.
6. Allen, E. V., and Camp, J. D.: *Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection With a Radiopaque Substance*, J. A. M. A. 104: 618, 1935.
7. Veal, J. R., and McPetridge, E. M.: *Adequate Circulation in the Extremities. Arteriography as a Test for Determining Its Limits: Preliminary Report Based on Thirty Amputations*, J. A. M. A. 104: 542, 1935.
8. Horton, B. T.: *Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography*, Am. J. M. Sc. 187: 649, 1934.

9. Barker, N. W.: Spontaneous False Aneurysm of the Popliteal Artery: Report of a Case, *M. Clin. North America* 18: 613, 1934.
10. Allen, E. V.: Roentgenography of the Arteries of the Extremities With Thorotrast, *Proc. Staff Meet., Mayo Clin.* 8: 61, 1933.
11. Edwards, E. A.: The Status of Vasography, *New England J. Med.* 209: 1337, 1933.
12. Radt, P.: Eine Methode zur roentgenologischen Kontrastdarstellung von Milz und Leber, *Klin. Wchnschr.* 8: 2128, 1929.
13. Rigler, L. G., Kouchy, R., and Abraham, A. L.: The Effects of Thorium Dioxide Sol (Thorotrast) on the Human Liver, *Radiology* 25: 521, 1935.
14. Yater, W. M., Otell, L. S., and Hussey, H. H.: Hepatosplenography With Stabilized Thorium Dioxide Sol: A Follow-Up Study of Two Hundred Patients Examined Over a Period of Five Years, *Radiology* (in press).
15. Caldas, J. P.: Artériographies en série avec l'appareil radiocarrousel, *J. de radiol. et d'electrol.* 18: 34, 1934.
16. Allen, E. V.: How Arteries Compensate for Occlusion: An Arteriographic Study of Collateral Circulation, *Arch. Int. Med.* 57: 601, 1936.
17. Horton, B. T., and Ghormley, R. K.: Congenital Arteriovenous Fistula, *Proc. Staff Meet. Mayo Clin.* 8: 773, 1933.
18. Frieih, P., and Lévy, A.: Documente artériographiques sur des dystrophies artérioveineuse des dysplasies neuroectodermiques congénitales, *Lyon chir.* 32: 43, 1935.
19. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, *Am. J. M. Sc.* 186: 493, 1933.
20. Hammon, L., and Rienhoff, W. F., Jr.: Subacute Streptococcus Viridans Septicemia Cured by Excision of an Arteriovenous Aneurysm of the External Iliac Artery and Vein, *Bull. Johns Hopkins Hosp.* 57: 219, 1935.
21. Frieih, P., and Lévy, A.: Aneurysmographies au Thorotrast, *Lyon chir.* 32: 161, 1935.

# THEORETICAL CONSIDERATIONS REGARDING THE VARIATIONS OF THE RS-T SEGMENT AND SUBSEQUENT T-WAVE FOLLOWING LOCAL VENTRICULAR TRAUMA\*

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IN A PREVIOUS paper<sup>1</sup> it was shown that a correlation exists between the electrocardiographic curves consequent to artificial stimulation of specific areas on the cat's ventricles and the later RS-T alterations resulting from cauterization of these same areas. From an examination of any one site, it was found that the main initial deflection of the extrasystolic wave was always opposite in phase to that of the RS-T alteration. The purpose of this paper is to demonstrate the significance of the relationship existing between these different portions of apparently dissimilar graphs and to show how conclusions drawn therefrom may be of value in advancing our understanding of the nature of the RS-T deviation and the subsequent T-wave variations following localized ventricular trauma.

## THEORETICAL CONSIDERATION OF RS-T ALTERATIONS

In order to explain this inverse relationship regarding the direction of initial extrasystolic waves and subsequent RS-T deviations, it is necessary to review the well-known monophasic electrocardiograms obtained from excitation of injured cardiac muscle strips. This explanation depends upon the fundamental principle, the basis of all the present concepts of tissue activation (Lewis, Craib, Eyster, Macleod), that tissue in an excited state is relatively negative to tissue in a resting state.

As is generally known, upon stimulation of a theoretically uninjured cardiac muscle strip at either end (*1a*, Fig. 1), a diphasic electrocardiogram is recorded in which there is a prominent initial wave, an intervening isoelectric period due to a balance of potential differences, and a terminal wave of lower amplitude whose excursion is opposite to that of the initial wave. The direction of both waves, however, will depend upon the connections with the string galvanometer and upon which end of the muscle strip is excited. Since the end stimulated is the first to manifest negativity, *1b* is recorded when the muscle strip at point *A* is activated and *1c* is recorded when the strip at point *B* is activated. If

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the quiescent muscle strip is injured at *B*, and injured-uninjured lead-offs are taken, a demarcation current or current of injury is recorded (*1d*) which persists so long as dying tissue is present. Upon excitation of any part of this injured strip, a diminution or negative variation of the current of injury now manifests itself. The string, which has been displaced from the isoelectric line by the demarcation current, tends to approach it and a monophasic type of curve (*1e*) is recorded during the excitatory period. The direction of this excursion is constant despite variations in the site of application of the stimulus.<sup>1</sup> Since in the usual operation of the electrocardiograph, constant currents, such as the injury current, are eliminated by the compensation of the string, *1f* is obtained instead of *1e*, and so only the negative variation of the current of injury is ordinarily exhibited (*1f*).

Certain conclusions can be drawn from a study of these electrograms. In line with the concept that injury to muscle tissue causes similar elec-

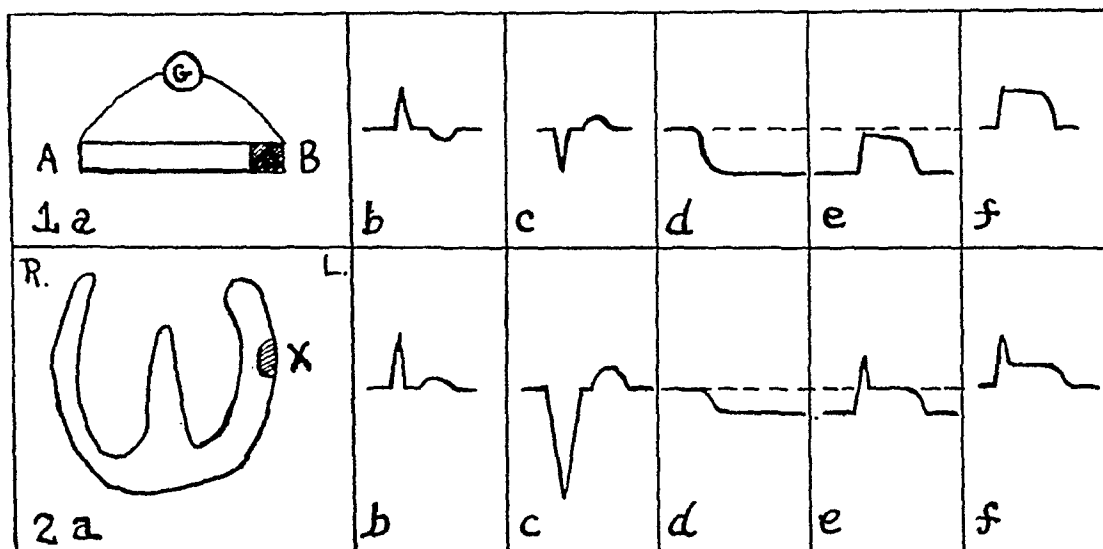


Fig. 1.—In *1a*, the simple cardiac muscle strip A-B is so connected to the galvanometer G that relative negativity at A causes an upward excursion of the string. In *2a*, the frontal section of the heart is connected to the galvanometer by means of the standard indirect Lead I. The deflections are explained in the text. The dashed horizontal line represents the theoretical isoelectric line of the galvanometer. The dark area in each diagram represents the relative size of the injured tissue.

trical reactions as does activation of muscle tissue, it is noted that the initial wave of the electrocardiogram (*1c*), caused by stimulation at point *B* before injury, is in the same direction as the current of injury (*1d*) resulting from trauma to this site (*B*). Since the monophasic wave obtained upon stimulation of the traumatized muscle (*1e*) (or *1f* after compensation) represents the negative variation of the existing current of injury, it is in opposite phase to the simple current of injury (*1d*); and it, therefore, must be in opposite phase to the initial deflection of the curve (*1c*) obtained by stimulation of the site (*B*) before the injury.

The frontal section of the heart (*2a*) may be regarded as a coiled and distorted thick muscle strip connected to the galvanometer by an indirect lead such as the standard Lead I. Normal cardiac activation is a balance

between almost simultaneous right and left ventricular excitation and, in Lead I, often produces a record such as *2b*. Upon stimulation at *X* on the surface of the left ventricle, a downward initial wave (*2c*) is observed in the electrocardiogram. If it were possible to obtain a record with the heart momentarily free of excitation *2d* would be registered on cauterization at *X*. The direction of this deflection would be negative because the negative pole of the demarcation current is oriented nearer to the left arm electrode. If, after such an injury, normal sinus rhythm is again recorded, *2e* would be obtained, and with string compensation *2f* would be observed.

Comparison between *2b* and *2f* reveals a difference in the contour of the graph consisting of a plateau instead of an isoelectric period between the R- and T-waves. This plateau is recognized as the RS-T change following injury to the heart muscle and is the counterpart of the monophasic type of curve (*1f*) obtained with excitation of the injured muscle strip, and recorded by direct leads. Since, under these conditions, the direction of the RS-T excursion is merely the result of a decrease or neutralization of the fixed demarcation current, it can be seen that the type of deviation is constant regardless of the source of cardiac excitation subsequent to the burn. Samojloff,<sup>2</sup> Parkinson and Bedford,<sup>3</sup> and Crawford and his coworkers<sup>4</sup> have all looked upon the RS-T change as a decrement of the current of injury.

It is evident that the initial wave resulting from stimulation at *X* before the cauterization (*2c*) is in an opposite phase to the RS-T deviation observed after trauma to the same site (*2f*); and furthermore that it is in the same phase as the demarcation current (*2d*). This, therefore, conforms with the theory that both excitation and injury are related electrical processes. There is this difference, however, that while the demarcation current is essentially a local phenomenon, the initial wave of the extrasystole represents the activation wave traveling from the point of stimulation not only through the underlying muscle wall, but also through the remainder of the ventricles. Since the heart may be assumed to approximate grossly a muscle shell (Wilson and his coworkers<sup>5</sup>), the average direction of the excitation wave penetrating from epicardium to endocardium will usually also correspond with its average or resultant direction through the rest of the heart. It can thus be understood why the entire initial deflection of the extrasystole is usually in the same phase as the local demarcation current and in the opposite phase to the subsequent RS-T change.

These theoretical considerations are supported by our experiments<sup>1</sup> in which it was found that the initial extrasystolic waves, obtained by stimulating the heart at any area, were opposite in direction to the RS-T changes recorded after burning the same region. This correlation usually was present for all three leads. Moreover, in the case of the extrasystolic complexes recorded from various sites of stimulation sub-

sequent to the cauterization of any one ventricular site, it was found that there was a displacement in the normally short isoelectric period existing between the initial and terminal deflection. The direction of this alteration depended solely upon the location of the injury, the change in all curves being in the same direction in any one lead, regardless of whether the activation of the heart arose from the sino-auricular node or from any point of stimulation on either ventricle.

#### COMPARISON OF EXTRASYSTOLES AND RS-T CHANGES IN THE HUMAN HEART

It is realized that the architecture and position of the heart relative to the standard limb leads are not alike in man and in the cat, and that experimental data on electrocardiographic localization of sites of stimulation and cauterization cannot therefore be wholly transposed from one to the other. However, the correlation of extrasystolic curves and RS-T changes, drawn from the observations in the cat's heart, is dependent upon electrical properties inherent in all myocardial tissue and may, therefore, apply equally as well to the human heart.

In order to apply this relationship to clinical cardiac infarction, it is necessary to review the extrasystolic complexes obtained upon excitation of the human heart. Upon stimulation at the left apex anteriorly, Barker and his associates<sup>6</sup> recorded negative main initial ventricular complexes in all three leads, the negativity being least in Lead III. Above this point but still within the lower half of the left ventricle, the complex of Lead III alone became transitional between negative and positive. In accordance with the correlation mentioned above, infarction at the apex of the left ventricle anteriorly would be expected to yield positive RS-T deviations in Lead I and Lead II and possibly in Lead III. With some upward extension of the infarct, RS-T<sub>3</sub> would become isoelectric or even negative. These predicted changes thus seem to conform with the T<sub>1</sub> type of electrocardiogram usually observed with infarction in this region and also with the common variation of the T<sub>1</sub> type.

Upon stimulation of the posterior surface of the human left ventricle, Barker and his coworkers again recorded prominent negative initial extrasystolic complexes in all three leads. An infarction in this region might then be expected to produce RS-T elevations in all three leads. However, the most frequent site of infarction in the posterior wall of the left ventricle is usually near the septum and sometimes the involvement extends partly over to some right ventricular musculature. This site may lie in part to the right of the transitional line for Lead I,\* and extrasystoles obtained from here would probably demonstrate isoelectric or

\*From a systematic application of stimuli to the epicardial surface of the cat's ventricles, Abramson and Weinstein<sup>7</sup> were able to plot a line of transition for the extrasystolic complexes recorded in Lead I. The initial extrasystolic complexes were positive to the right of the line and negative to the left of the line. This line, running almost vertically down over the anterior surface of the heart and then curving around the apex to extend upward over the posterior surface, was situated on the left ventricle near the septum in most of its course.

even positive initial complexes in Lead I. Hence it can be seen that an electrocardiogram of infarction in the latter region would reveal elevation of RS-T<sub>2</sub> and RS-T<sub>3</sub>, whereas RS-T<sub>1</sub> might be isoelectric or even negative. It is evident that such a graph is similar to the clinical T<sub>3</sub> type of record obtained with the most frequent site of infarction in the posterior wall of the left ventricle.

Certain inferences may be drawn about localization of clinical myocardial infarction if the data obtained in the cat's heart are more broadly applied. In anterior infarction the RS-T<sub>3</sub> displacement depends upon the caudocephalic relationship of the infarct in the left ventricle, cephalic extension producing a negative RS-T<sub>3</sub> and caudal localization producing a positive RS-T<sub>3</sub>. In anterior infarction of the left ventricle RS-T<sub>1</sub> and RS-T<sub>2</sub> are usually positive. In posterior infarction the RS-T<sub>1</sub> displacement depends upon the extent of the infarction to the right or left of the line of transition for Lead I, mentioned above, extension to the right yielding a negative RS-T<sub>1</sub>. RS-T<sub>2</sub> and RS-T<sub>3</sub> are ordinarily positive in posterior infarction of the left ventricle. Accordingly, the frequently observed reciprocal relation of RS-T<sub>1</sub> and RS-T<sub>3</sub> displacements in individual clinic records appears to us to be merely fortuitous.

#### THE VARIATIONS OF THE T-WAVE FOLLOWING MYOCARDIAL INFARCTION

It is readily appreciated that the RS-T deviation from the isoelectric line persists only so long as the current of injury endures. In patients with myocardial infarction, the subsequent electrocardiograms during a temporary interval of weeks or even months usually reveal a prominent coved and peaked T-wave, whose direction is opposite to that of the previous RS-T alteration. This sequence may be explained by a further application of the theoretical considerations presented above.

With vascular occlusion the injured myocardium manifests a current of injury only during the initial stage of degeneration, since dead muscle fibers are electrically inert. As healing in the infarct occurs, the absolutely destroyed muscle becomes replaced with fibrous tissue, and the other part returns to a normal state sooner or later. As Parkinson and Bedford<sup>3</sup> have remarked, there exists in all probability a zone of transition, exhibiting impaired circulation, between the normal myocardium and the site of actual necrosis. It is reasonable to assume that in this intermediate zone, the zone of reactive inflammatory changes, there may be some impairment of myocardial function with a concomitant delay in the electrical processes of both activation and retreat.

Delay in retreat in this transitional zone may account for the coved or "coronary" T-wave. The comparatively low voltage of the normal T-wave is the result of a partial balance, and the preceding isoelectric interval a result of complete balance, of opposing electropotentials exist-

ing simultaneously throughout the major portion of the heart during the recovery period. As Katz<sup>8</sup> has pointed out, the actual direction of the T deflection is probably determined by that part of the heart in which the electropotential endures the longest. When any pronounced local retardation in recession appears, its electrical effects are practically unopposed by those of earlier retreat in the rest of the heart; and one of the possibilities of such an imbalance is the production of a T-wave of greater magnitude and of different contour and direction. It is reasonable to assume that the negative potential in the activated muscle mass would persist longest in the intermediate zone with impaired circulation, discussed above, and that the "coronary" T-wave would therefore be due to the delayed and consequently unopposed electropotential present in this zone. Furthermore, since the direction of the original current of injury was also the result of negative charges in the same location and orientation, it follows that its theoretical registration and that of the "coronary" T-wave would both be in the same phase. Since the RS-T alteration obtained during the acute stage was a decrement of the current of injury and thus in opposite phase, it can be understood why the direction of this RS-T alteration similarly is inverse to that of the subsequent "coronary" T-wave.

To illustrate this relationship and to demonstrate that the theory of doublets and their limited potential differences may also apply, a specific area of the heart, such as the apex of the left ventricle, will be considered. Because of the site chosen, the normal potentials of excitation and retreat travel downward and to the left through this region. If it were possible to record only their local electrical effects, the initial deflections (representing excitation) would be positive, and the terminal deflections (representing retreat), negative in at least Lead I and Lead II. At this site the initial deflection of Lead III would be either positive or negative, and, hence, for simplicity, this lead is not included.\* It is generally known that acute infarction of the apex of the left ventricle produces RS-T elevations in the first two leads and subsequent T-waves which are negative. The direction of these T-waves is, therefore, similar to that of the above mentioned terminal deflections normally arising from this local site during retreat. In consequence thereof, the "coronary" T-wave is necessarily due to a predominance of the recovery factor in this region caused, most likely, by the delay in retreat incident to the infarction here.

Craib<sup>9</sup> has made the assumption that the "coronary" T-wave is due to the entire absence, during recovery, of the normal electrical effects in the infarcted region. If this were so, then the balance during re-

\*With the customary Einthoven equilateral triangle constructed from the three standard leads, an excitation vector directed downward and to the left produces positive projections on the lines of Lead I and Lead II. The projection on the line of Lead III is either positive or negative, depending, respectively, upon whether the vector is oriented clockwise or counterclockwise to the perpendicular of the line of Lead III. With the reversal of the charges of the advancing doublet during the period of recession, a recovery vector directed downward and to the left produces negative projections on the lines of Lead I and Lead II.



covery would swing in the opposite direction; and with the normal negative terminal components of Lead I and Lead II missing from the infarct at the apex of the left ventricle, the "coronary" T-waves would become more elevated than the normal T-waves, and thus be recorded in the same direction as the previous RS-T alterations. Craib's assumption in reference to the usual "coronary" T-waves of several weeks' duration accordingly does not seem applicable. The most satisfactory explanation for the origin of the "coronary" T-wave, it seems to us, is that it is a result of the retardation of recovery in the living muscle tissue with impaired nutrition, lying in the zone between the actual necrosis and the normal heart muscle. With the return of metabolic conditions in this intermediate zone to normal, the "coronary" T-wave gradually may become replaced by a normal T deflection.

However, curves of acute infarction, showing large T-waves in the same phase as RS-T alterations and occurring for a short time after the acute insult, have been reported and can be explained by the supposition that part of the affected myocardium is in a state of shock and consequently inert electrically, while the other more severely damaged part produces only the current of injury.

#### SUMMARY

1. The theoretical basis is presented for the correlation, observed in the cat's heart, that the initial deflection of the extrasystolic wave, recorded with artificial stimulation upon a specific site, is in opposite phase to the RS-T change, recorded with cauterization of the same site.
2. This correlation seems applicable to the human heart. It may explain the variations in the relationship of the RS-T displacement in the first and third leads.
3. The usual characteristic T-wave of myocardial infarction is probably the result of a retardation of the process of retreat in the living muscle tissue with impaired circulation, lying in the zone between the actual necrosis and the normal heart muscle.

#### REFERENCES

1. Abramson, D. I., Shookhoff, C., and Fenichel, N. M.: A Study of the Variations of the RS-T Segment in Experimental Ventricular Trauma, *AM. HEART J.* 12: 174, 1936.
2. Samojloff, A.: *Pfuger's Arch. f. d. ges. Physiol.* 135: 417, 1910.
3. Parkinson, J., and Bedford, D. E.: *Heart* 14: 195, 1927-29.
4. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: *AM. HEART J.* 7: 627, 1932.
5. Wilson, F. N., Macleod, A. G., Barker, P. S.: *AM. HEART J.* 6: 637, 1931.
6. Barker, P., Macleod, A. G., and Alexander, J.: *AM. HEART J.* 5: 720, 1930.
7. Abramson, D. I., and Weinstein, J.: A Basis for the Analysis of Variations in the Form of Electrocardiographic Curves Resulting From Experimental Premature Contractions, *Am. J. Physiol.* 115: 569, 1936.
8. Katz, L. N.: *Physiological Reviews* 8: 447, 1928.
9. Craib, W. H.: *The Electrocardiogram*; Medical Research Council; London, 1930, His Majesty's Stationary Office.

# APPLICATION OF ROENTGENKYMOGRAPHY TO THE STUDY OF NORMAL AND ABNORMAL CARDIAC PHYSIOLOGY\*

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**R**OENTGENKYMOGRAPHY is a method of recording graphically visceral movement by the x-ray. The technic and the general principles of application of this method to the study of the heart have been dealt with in other communications.

Roentgenkymography of the heart gives a record similar to that obtained with the myocardiograph in animal experiments. Both inscribe cardiac movement, but the roentgen method, utilizing a beam of x-ray instead of a mechanical lever, gives a record which is freer from distortion.

The kymoroentgenogram of the heart is made by interposing between the patient and the film an impermeable sheet of metal in which there are slits 0.4 mm. in width, spaced 12 mm. apart. The film is not stationary as in the ordinary roentgenogram, but moves at right angles to the direction of the slits during the exposure. Actually the movement of only those portions of the heart surface are recorded which are opposite the slits, thin bands 0.4 mm. wide and 12 mm. apart. This spacing is, however, sufficiently close to give information regarding all those portions of the heart which contribute to the make-up of the cardiovascular shadow. To avoid overlapping of the records, the film is moved just short of the distance between the slits (Fig. 1). The film is standardized to move 12 mm. per second, and the exposure is one second, thus recording one or more complete cycles. The time may be read on the distance axis.

If the movement of that portion of the heart shown in the slit is more or less parallel to the direction of the slit, it is recorded in the form of a wave. If the point has no movement or if the movement is at right angles to the direction of the slit, the contour shows a straight edge without waves.

The form of the wave with a definite rate of film motion depends on the character of the movement of the particular point of the heart. The legs of the waves may be straight or curved depending on the speed of motion. A very sharp peaked wave is produced by an extremely rapid movement and change in direction. The movement may be so fast that its record is practically a horizontal line. A domelike wave represents

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a slow change in direction, a progressive increase and diminution in the speed of movement—a motion similar to that of a swinging pendulum. When the to-and-fro motion is not regular, the motion being faster in one direction, the faster motion produces a straightening and shortening of the particular leg of the wave. Imposed on these waves are angulations, hooks, peaks, indentations, and terraces, representing the rapid changes in the direction of the movement of the cardiac muscle, movements of the heart as a whole, and local vibrations produced by currents of blood within the heart.

It is obvious that the outward thrust of the heart action (diastole) produces one side of the wave and the inward thrust (systole), the other. The crest of the wave represents the end of diastolic period or

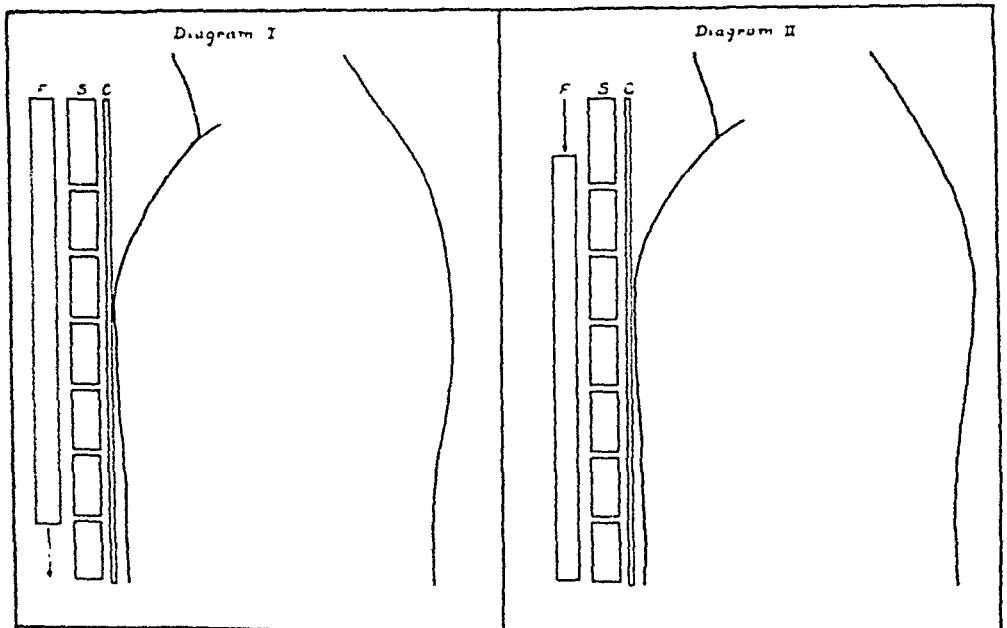


Fig. 1.—*S*, lead sheet with slits; *F*, cassette and film which move downward a distance slightly less than the distance between slits. Diagram I, before exposure, and Diagram II, after movement of the film and its exposure.

beginning of systolic, while the deepest portion of the trough represents the period of maximum systole or the beginning of diastole.

Since the film moves downward, the flow of the time is upward. The waves differ in morphology depending on the chamber of their origin. The altitude of the wave represents more or less accurately the amplitude of movement; the abscissa the duration of movement. Recorded during the same fraction of time, the time relationships of the various waves are directly comparable. The analysis of the time relationships is limited by a time resolution of 0.02 sec.

Figure 2 is a typical kymogram of a normal heart. It is obvious that the waves differ in appearance over different parts of the cardiac shadow and are characteristic for each chamber, thus providing a method for topographic analysis of the cardiac contour. It is not necessary to en-

ter here in detail into the contribution which this method of examination makes to the analysis of the composition of the cardiac silhouette. It is sufficient to point out that, contrary to the usual x-ray and anatomical interpretation, the right ventricle appears to participate in the formation of the lowermost portion of the right cardiac contour in a large proportion of normal hearts. Definite ventricular waves practically similar to the ventricular waves on the left side have been found in 75

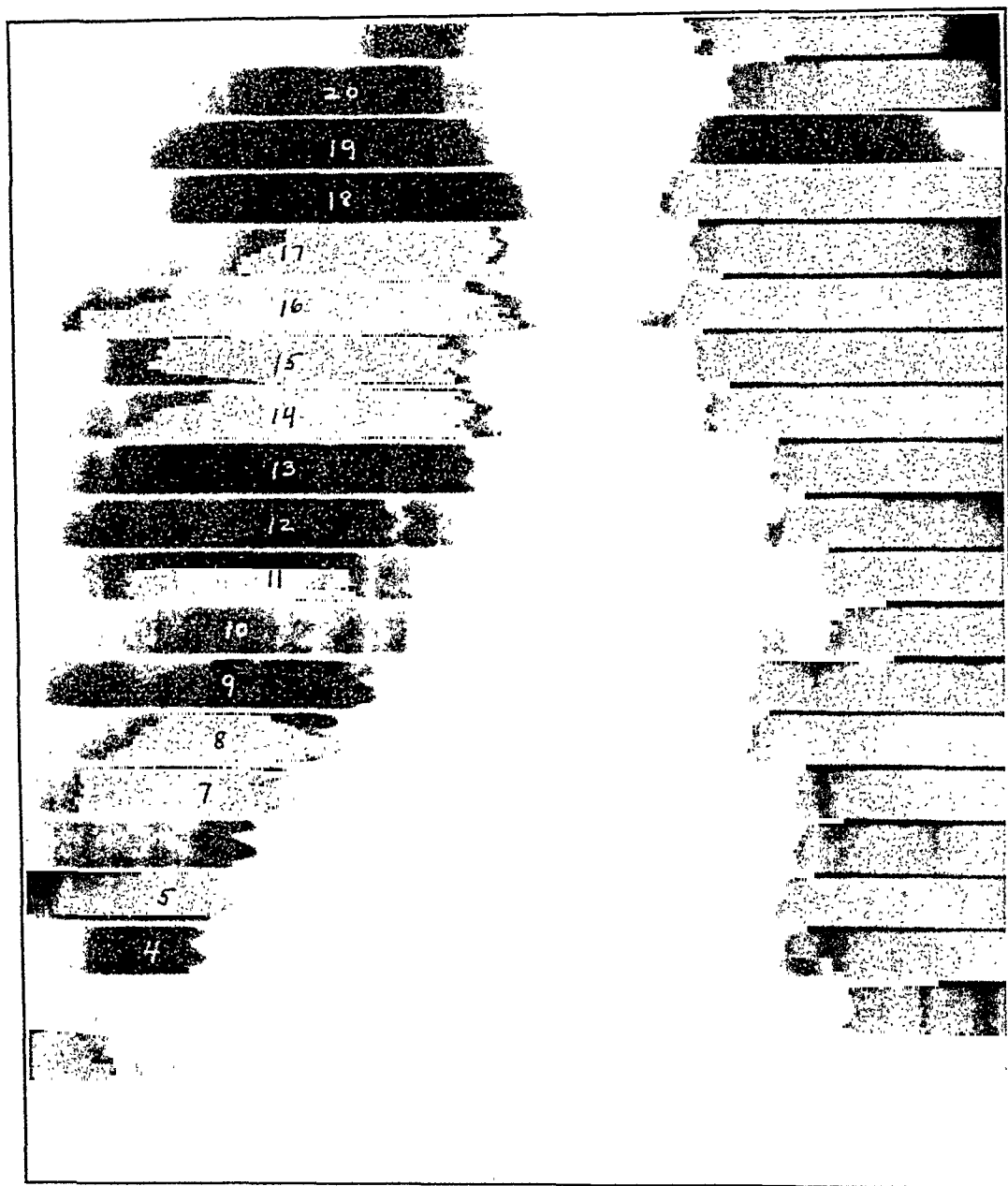


Fig. 2.—Roentgenkymogram of a normal heart. The waves over the entire cardiac shadow are movement records of the particular portions of the heart and its great vessels. The peak of the wave represents the particular part in maximum diastole or dilatation while the deepest point in the valley represents the position of the particular part in maximum systole or retraction. Waves of different shape and size may be distinguished over different portions of the cardiovascular shadow, corresponding to the chamber of their origin. Since the duration of the x-ray exposure is one second, the distance between the black lines may be divided into as many parts as is desired representing fractions of a second. By laying off on the waves of each band a definite distance, corresponding to a certain fraction of time and connecting these homologous points, the shape and outline of the heart at that particular instant may be shown.

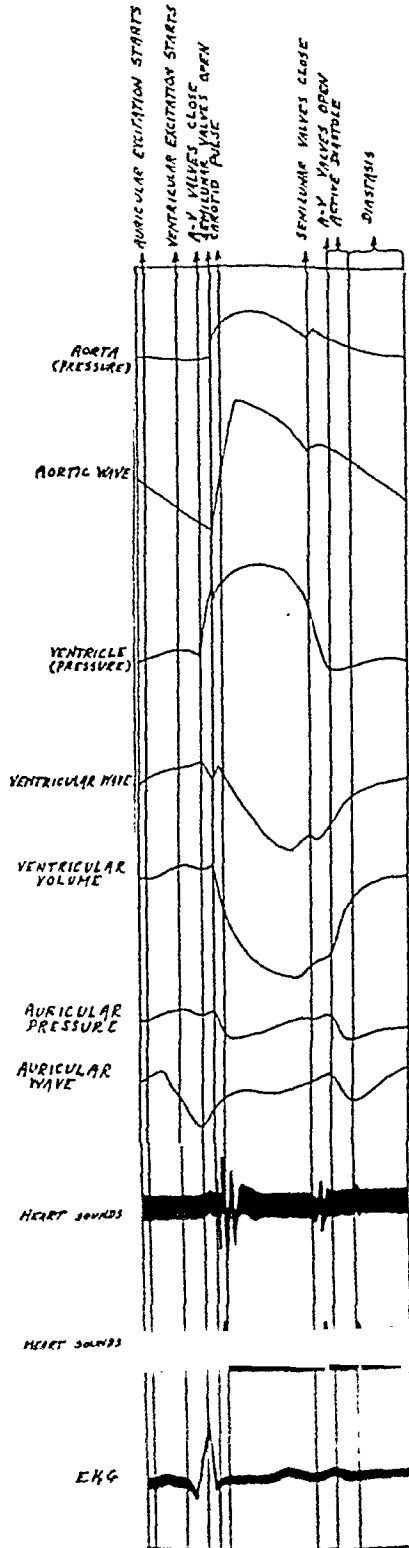


FIG. 3.—Diagrammatic representation of relation of kymographic wave record to the record of other events of the cardiac cycle. The movements of the different chambers may be graphically correlated and the relation of the kymographic waves to each other and to other events in the cardiac cycle. The time relations of the kymographic waves have been checked with simultaneously recorded electrocardiograph and heart sounds and on this basis the waves may be assigned to specific events in the cardiac cycle. In fig. 5 is a graphic correlation of the waves of various chambers with a simultaneously recorded electrocardiograph.

per cent of young adults. Further, the portion of the cardiac contour above the right auricle is generally taken to represent the ascending aortic arch. However, in 180 normal hearts, aortic waves were present in only 20 per cent. In the majority of cases this portion of the cardiovascular contour is apparently formed by the superior vena cava.

The movements of the different chambers may be graphically correlated by charting the relationship of the kymographic waves to each

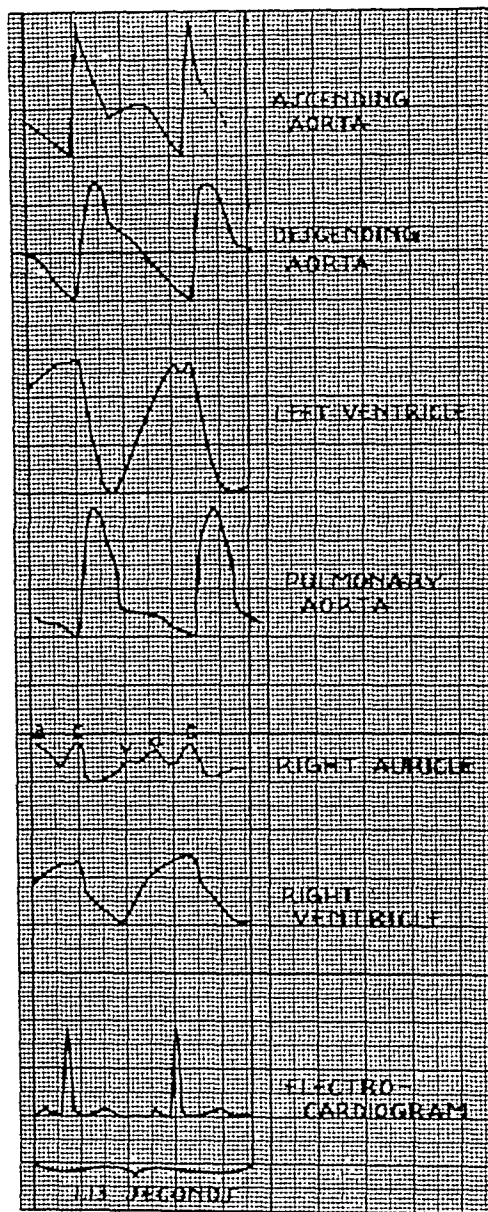


Fig. 4.—Graphic correlation of kymographic waves from a normal kymogram.

other and to other events in the cardiac cycle on the same time axis as is diagrammatically represented in Fig. 3. The time relations of the kymographic waves have been checked with simultaneously recorded electrocardiogram and heart sounds, and on this basis the waves may be assigned to specific events in the cardiac cycle. Figure 4 is a graphic correlation of the waves of the various chambers, with a simultaneously recorded electrocardiogram.

## VENTRICULAR WAVES

This wave consists fundamentally of a sharp, smooth inward limb representing systole, followed by a bent limb representing diastole. The amplitude of the wave does not, however, always represent the true amplitude of motion of the particular point of the ventricular contour. The kymogram records accurately only that component of motion parallel to the slit; movement at an angle to the slits is somewhat distorted and exaggerated.

If the motion is not parallel to the direction of the slits, as is the case with the greater portion of the left cardiac border, particularly in cases in which the upper part of the contour runs very obliquely to the direction of the slits, the amplitude may be determined by projecting corresponding peaks and troughs of two bands to the horizontal line bounding each band and connecting these projections. The perpendicular distance between these lines is the amplitude, but not the exact amplitude, for with a target-film distance of 100 cm. there is still some magnification of the image.\*

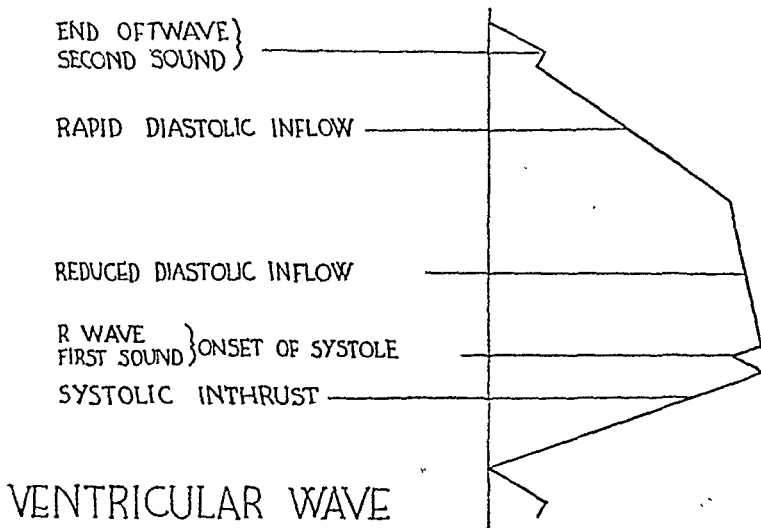
The ventricular wave bears a close resemblance to ventricular volume curves experimentally recorded with the cardiometer. Some, impressed by the close correspondence, regard the kymographic wave of the left ventricle as practically a pure volume curve, and with restrictions accept differences in amplitude of the wave as indices of the changes in stroke volume. Quantitatively, however, the change in cardiac contour, which the kymogram records, is not purely a volume change, but is the resultant of the predominant contractile thrust, of rotary movements, and of motion of the heart as a whole. Besides this there is the motion of the atrioventricular septum which is not at all represented in the movements of the outer contour.

This criticism applies, of course, not only to the kymographic, but to all x-ray technics of studying cardiac motion, viz., fluoroscopy, cinematography, and systole-diastole exposures, and reveals the fundamental inaccuracy of attempting to estimate changes in heart volume from changes in the area of the cardiac shadow as has been advocated by Bardeen<sup>1</sup> and by Eyster and Meek.<sup>2</sup>

The diastolic limb of the ventricular wave (Fig. 5) at ordinary resting rates of from sixty to eighty shows a break at about its middle, the later half of the wave being somewhat flattened. The first major segment of the diastolic limb corresponds to the period of early rapid inflow. The break in the limb indicates a reduced rate of filling, i.e., the period of diastasis preceding contraction. Auricular systole, which occurs during this period of diastasis, does not usually modify perceptibly the diastolic wave and does not appear to contribute significantly to

\*While the shorter focal distance prevents teleroentgenographic measurements, it nevertheless has the advantage of emphasizing by slight magnification the more delicate and less perceptible portions of the wave.

ventricular filling, although occasionally a distinct outthrust on the diastolic limb may be observed simultaneously with the intrust of the auricular wave. When the heart rate is rapid, the break in the diastolic limb disappears; there is no period of diastasis; and the filling continues uninterruptedly to the beginning of the next systole. Under these circumstances auricular systole contributes significantly to the filling of the ventricle, for the ventricle is not yet full when auricular systole takes place.



### VENTRICULAR WAVE

Fig. 5.—Graph showing the relationship of movement to conduction phenomena.

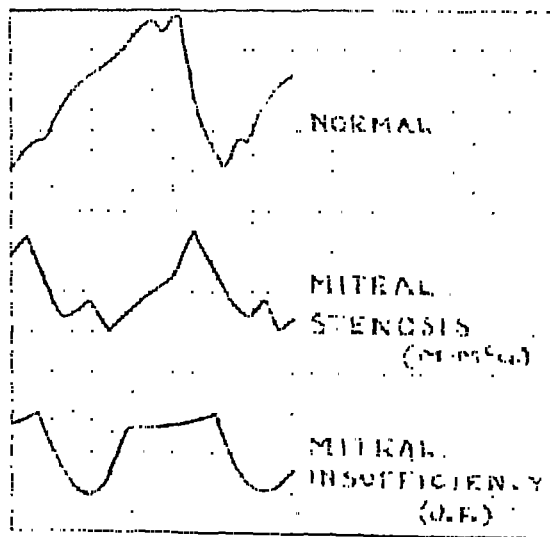


Fig. 6.—Graph transposed from kymograms showing the waves of left ventricle in the normal state, in mitral stenosis, and in mitral insufficiency.

The rapid inflow into the ventricle in early diastole occurs as a consequence of the accumulation of blood in the auricle during the ventricular systole while the atrioventricular valves are closed. When the valves are opened, the inflow into the ventricle takes place with a sharp sudden fall in auricular pressure.

In mitral insufficiency the first dynamic event is congestion in the left auricle, which precedes further back pressure effects into the pul-



monary artery, right heart, and great veins, the mean pressure in the pulmonary artery usually not being measurably affected (McCollum and McLure<sup>12</sup>). When the insufficiency is uncomplicated, the pressure in the left auricle is increased markedly during ventricular systole because of the regurgitation. The rate of inflow into the ventricle in early

Fig. 7

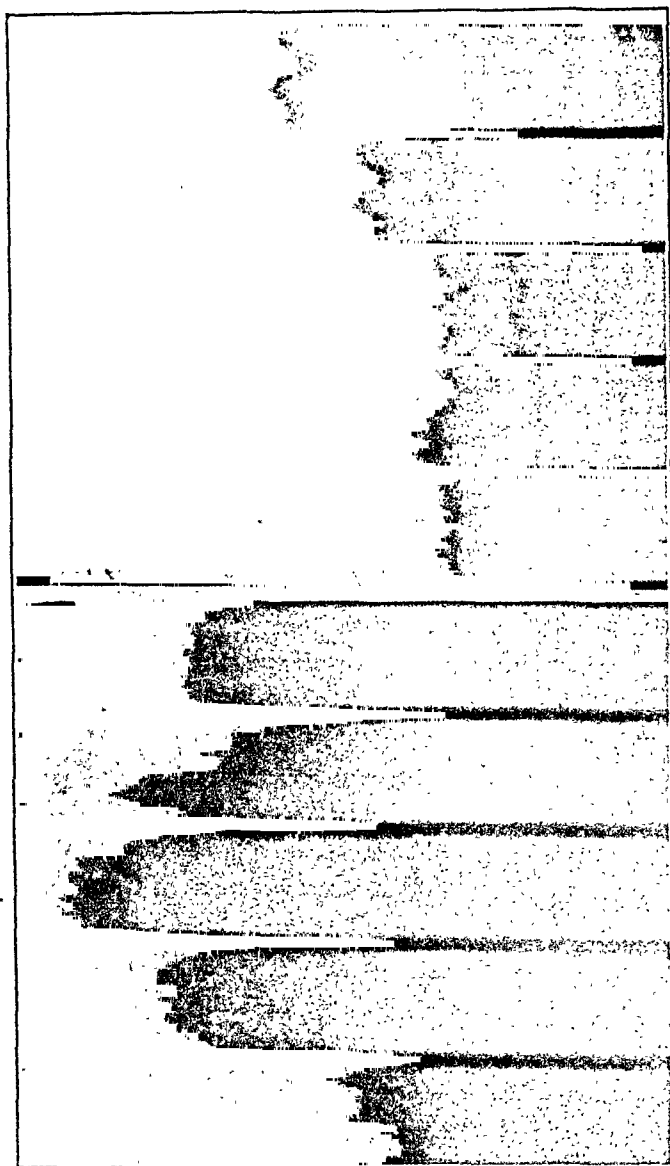


Fig. 8.

Fig. 7.—Mitral insufficiency, ventricular filling abrupt and almost completely in early diastole. Clinically diagnosis of mitral stenosis was made on basis of loud systolic and diastolic murmurs at apex, with presystolic murmur and thrill at mitral area. Post-mortem examination revealed a greatly widened mitral ostia with no evidence of any stenosis.

Fig. 8.—Mitral stenosis. Delayed filling of left ventricle, most of filling occurring at end of diastole due to auricular systole. The ventricular movement is of small amplitude. Typical buttonhole mitral stenosis found at autopsy.

diastole is accordingly accelerated. There is practically complete filling in the early inflow phase. This, as pointed out by Hirsch, is revealed

in the ventricular wave by a rapid, outwardly directed limb in the early inflow phase of diastole. It is succeeded by a long period of diastasis. The two phases of the diastolic limb are thus differentiated by a sharp angulation (Fig. 6).

In mitral stenosis, on the other hand, although the left auricular pressure is also increased, early diastolic inflow is impeded because of the narrowed atrioventricular orifice, and the filling is slow and gradual throughout diastole, with no period of diastasis (Fig. 6). Under these circumstances, auricular systole may contribute significantly to ventricular filling. The diastolic limb of the ventricular wave is an unbroken line of low amplitude and attains its maximum height late in diastole.

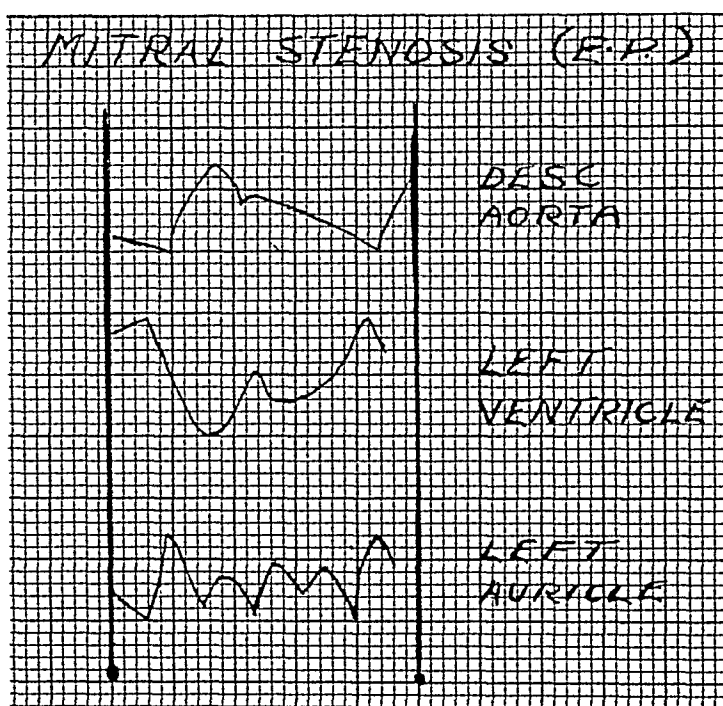


Fig. 9.—Mitral stenosis. Graph showing the typical late ventricular filling and the diminished aortic movement.

When both lesions coexist, the filling curve varies from the insufficiency to the stenotic type depending on which process predominates. It is generally known that detection of an organic stenotic lesion as evidenced by a diastolic apical thrill and murmur does not necessarily signify dynamic mitral stenosis. The characteristic dynamic changes are, according to Wiggers, produced only by excessive degrees of stenosis, a very considerable degree of narrowing (approximately to one-quarter natural size), being required before the increase in resistance fails to be compensated for by the rise of left auricular pressure which naturally follows.

The kymographic examination may thus assist in the clinical differentiation of the dominant lesion, in the presence of signs indicating

double mitral disease. In Figs. 7 and 8 are reproduced the ventricular kymographic waves of two cases, each clinically diagnosed as double mitral disease. The kymographic diagnoses based on the study of the waves of the left ventricle, in one, of mitral insufficiency (Fig. 7), and in the other, of mitral stenosis (Fig. 8), were confirmed by autopsy.

The graphic transcription in Fig. 9 illustrates clearly the delayed filling of the left ventricle in mitral stenosis; the case being that of

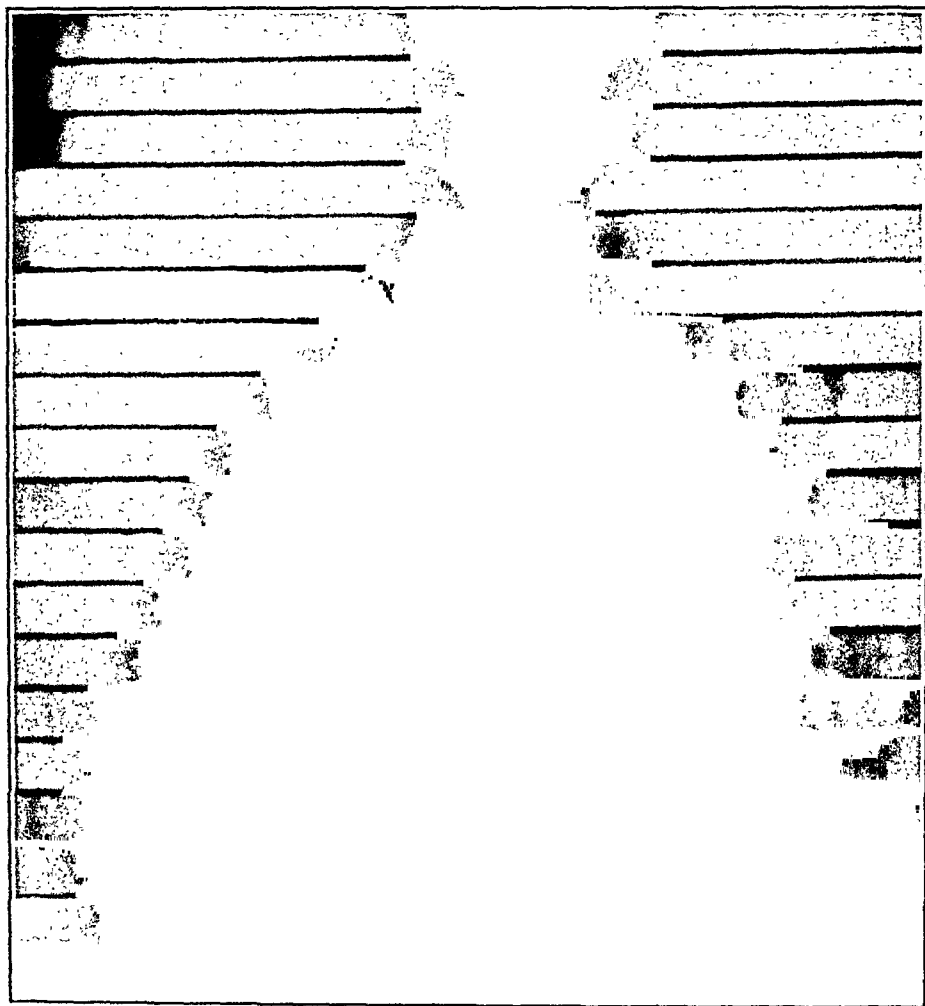


Fig. 10.—Kymogram. Mitral insufficiency.

a thirty-three-year-old woman, with a twenty-eight-year history of rheumatic activity, presenting all the clinical features of mitral stenosis.

Figure 11 shows a graphic correlation of the waves from a kymogram of advanced mitral insufficiency (Fig. 10). The left auricle is markedly dilated, occupying a considerable portion of the left contour. The ventricular wave shows the accentuated early diastolic inflow characteristic of mitral insufficiency, followed by a long period of reduced filling. During ventricular systole the auricle is seen to fill to a greater degree

than normal, because of the regurgitation. The auricular waves otherwise resemble the right auricular waves found normally. The systolic outthrust of the aortic wave in this case is considerably slower than normal, indicating a reduced rate of ejection. This, according to Wiggers,<sup>17</sup> is the dynamic crux of mitral regurgitation, a heart remaining compensated in the face of a mitral leak so long as it is able to attain a

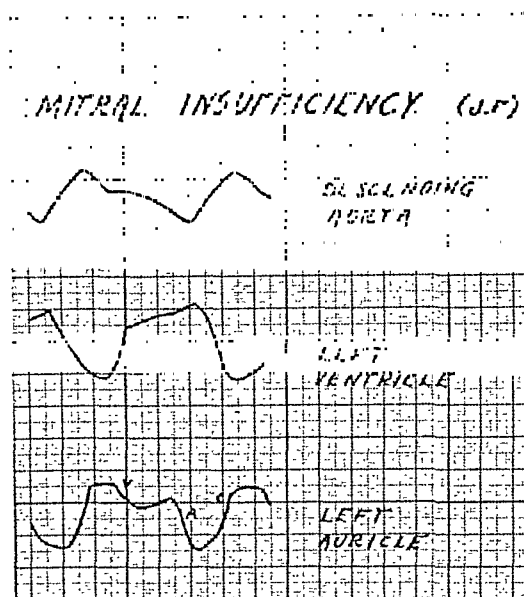


Fig. 11.—Graph from kymogram shown in Fig. 10, showing correlation of aortic, ventricular and auricular waves. The graph shows almost complete filling of left ventricle in early diastole, marked increase in left auricular volume coincident with systolic inthrust of the left ventricle and slow systolic outthrust of aortic wave as in aortic stenosis due to diminished rate of ventricular discharge into the aorta in consequence of mitral regurgitation.

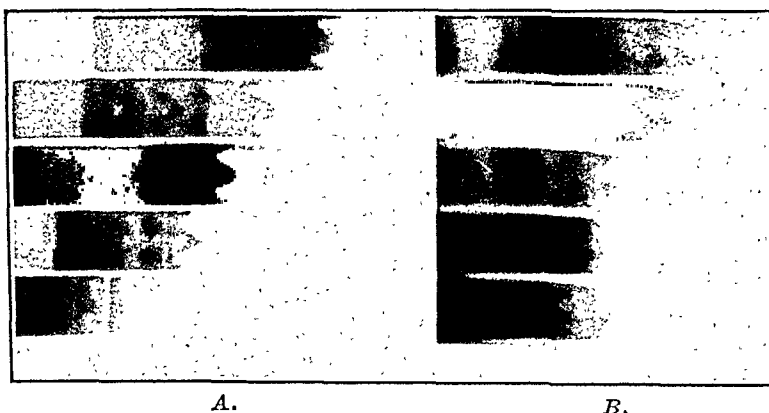


Fig. 12.—Development of mitral insufficiency in a child of eleven years. A, normal kymogram, taken upon admission for first attack of rheumatic fever. B, mitral insufficiency, six months later, showing ventricular wave characteristic of mitral insufficiency.

rapid rise of pressure isometrically and maintain a normal rate of discharge, decompensation setting in when a weakened myocardium cannot contract forcibly enough to raise its pressure rapidly, the pressure being dissipated through the mitral valve due to the regurgitation, with consequent diminished rate of discharge into the aorta.

The development of mitral insufficiency recorded kymographically, paralleling the clinical course, is shown in Fig. 12, *A* and *B*. The first kymogram, taken shortly after admission for a first attack of rheumatic fever, is normal, but the second, six months later, shows a decided modification of the wave of the left ventricle which indicates that the ventricle fills abruptly early in diastole and that this is followed by a long period of diastasis giving the wave the appearance characteristic of mitral insufficiency.

Superimposed on the main limbs of the ventricular wave are two small serrations. One is located immediately after the end of systole, appearing usually as a step at the beginning of the diastolic limb. This corresponds in time exactly with an incisura on the retracting limb of the aortic and pulmonary artery waves. The other serration is located at the peak of the ventricular wave, at the beginning of the systolic

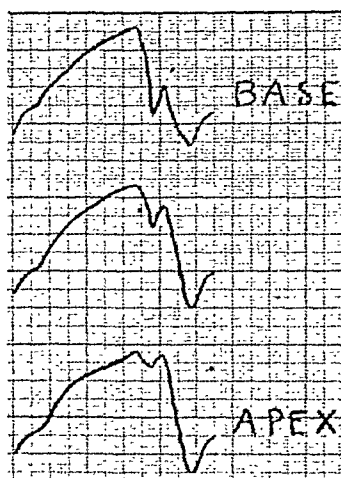


Fig. 13.—Variation of the ventricular wave from base to apex. The actual time of closure of the A-V valves is the same, but there is apparently a more vigorous movement at the base.

limb (Fig. 5). These serrations have been shown by Hirsch and Schwarzschild<sup>7</sup> to correspond exactly with the second and first heart sounds, respectively. Since the sounds are related to valve action, it appears likely that these waves are related to closure of the semilunar and atrioventricular valves.

The steplike serration simultaneous with the second heart sound at the beginning of the diastolic limb and corresponding precisely in time with the incisural notch of the vascular waves terminates simultaneously with the deepest point of the incisura, which marks the closure of the semilunar valves (Fig. 3).

The constant appearance of the serration as an outward step at the beginning of the diastolic limb and its simultaneity with the second heart sound and with the vascular incisura suggest that a perceptible regurgitation may take place physiologically at this time, i.e., before

the closure of the semilunar valves. Further evidence for this view is afforded by the fact that in aortic insufficiency this initial outward limb is greatly accentuated, appearing no longer merely as a small step engrafted on the main diastolic limb, but as a definite peak.

The serration simultaneous with the first heart sound appears as a double peak with an intervening notch, the total duration of this complex being about 0.08 sec. It is located essentially at the peak of the ventricular wave but undergoes progressive modification from the base to the apical portion of the ventricular contour, as seen in Fig. 13. Toward the base of the heart, the second peak is located on the systolic limb; over the middle and apical portion of the ventricular border, it lies closer to the apex of the ventricular wave. The time of this second

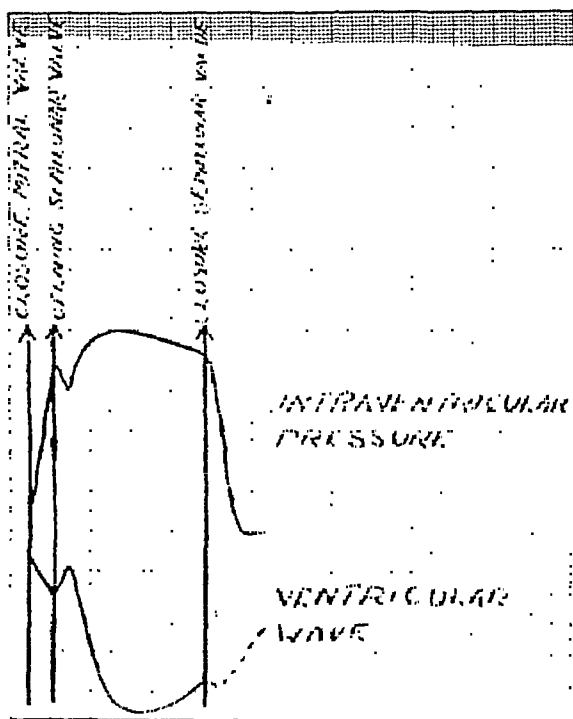


Fig. 14.—Correlation of ventricular kymographic wave with intraventricular pressure curve.

peak is the same over all portions of the ventricle despite changes in position. The trough between the two peaks is simultaneous with the onset of ejection as measured by the beginning outthrust of the aortic wave.

This complex cannot represent volume changes, for the first inward movement occurs during the isometric phase of the systole and simultaneous with the major component of the first heart sound, before ejection has begun. These rapid movements do, however, parallel and appear to reflect the changes in intraventricular pressure which occur at the onset of systole (Fig. 14).

During the isometric phase of systole there is a sharp rise of intraventricular pressure which transiently overshoots the aortic pressure due to inertia in the opening of the semilunar valve. With the opening of

the semilunar valve there is an abrupt decline to aortic pressure, the intraventricular pressure thereafter following aortic pressure for the remainder of systole.

The isometric overshoot of intraventricular pressure above aortic pressure appears to be directly proportional to the vigor of ventricular contraction, the overshoot disappearing in a weak ventricle, due to the lessened rate of increase in intraventricular pressure isometrically, giving the semilunar valve time to open before the aortic pressure is exceeded. It is significant that in myocardial degeneration the corresponding spike of the ventricular serration is greatly diminished or absent. It is also lost in mitral insufficiency where the regurgitation prevents an abrupt rise of intraventricular pressure.

The same sort of vibrations have been described by Tennant and Wiggers<sup>16</sup> experimentally with the myograph. This, however, is believed by them to be an artefact. It is interesting to note that in their myograms showing the development of myocardial damage following coronary occlusion these serrations disappear. Tennant and Wiggers suggest, consistent with the explanation offered above, that a local area of weakness may cause significant loss in the development of intraventricular pressure.

#### AURICULAR WAVES

The waves produced by auricular motion are multiple and of small amplitude. If the waves are graphically correlated with ventricular and vascular waves (Fig. 4), a definite sequence in their relation to ventricular and vascular waves is observed, which is constant not only in the same subject in different segments, in successive beats, and on different days, but in different subjects as well.

The left auricle is represented in the kymogram only by the auricular appendix which most often occupies but one segment, and the motion of the left auricle is therefore not well reflected, except in pathological dilatation in mitral disease.

The right auricular motion is far more constant, and there are typical waves over this portion of the cardiac contour. The information given by these waves is the same as may be obtained from auricular pressure records in animals and jugular pulse tracings in man.

The first of the auricular waves appears as an intrust terminating at the peak of the ventricular wave immediately preceding the onset of systole. It is simultaneous with the P-wave of the electrocardiogram (Fig. 4) and represents auricular systole. Its onset comes at about the peak of the P-wave and the duration varies from 0.08 to 0.12 sec. (a).

The second wave begins as a sharp outthrust with the onset of the isometric vibration complex of the ventricular wave which is simultaneous with the first heart sound. This wave is due to a reflection of ven-

tricular events. This outward motion in early systole corresponds to the abrupt rise in auricular pressure at the onset of the ventricular contraction which is due to back pressure from the ventricle in the closure of the atrioventricular valve. The immediately succeeding fall in auricular volume parallels a reduction in auricular pressure which Wiggers ascribes to a descent of the base of the ventricle, the brusque auricular traction reducing the pressure (c).

Following this inward thrust the auricle gradually increases in volume for the remainder of ventricular systole, as a result of inflow from the great veins. With closure of the semilunar valves, as indicated by the aortic incisura and ventricular serration corresponding to the second heart sound and the opening of the A-V valve, the auricular volume decreases sharply, corresponding to the rapid inflow phase into the ventricle (v).

The upper portion of the right cardiac contour is formed in the majority of cases in the young, not by the ascending arch of the aorta, but by the vena cava. In clear records in which the waves of the vena cava have sufficient amplitude to be analyzed, they closely parallel the auricular waves, with a time delay of a few hundredths of a second, which may be progressively traced, because of transmission of the impulse from the auricle up the vena cava (Fig. 18). The same three waves can be distinguished, and they form the a-, c-, and v-waves recorded in jugular pulse tracings. The kymogram thus confirms the now generally accepted interpretation of the origin of the c-wave of the jugular pulse, i.e., that it is due to transmission from the auricle and is not, as MacKenzie originally believed, a parasitic wave reflected from the carotid artery by reason of the close apposition of the jugular vein and carotid artery.

#### VASCULAR WAVES

The aortic wave consists of a sharp outthrust commencing simultaneously with the beginning of the systolic limb of the ventricular wave, succeeded by a blunt peak whose retraction terminates in the incisural notch. The onset of ejection is marked not only by the outthrust of the aortic wave, but a coincidental sharp increase in density of the aortic shadow as well. The time from beginning aortic outthrust to the depth of the incisural notch forms a convenient measure of the duration of ejection since it represents the time from the opening to the closure of the semilunar valves. There is a slight rebound from the depth of the incisural notch after which a gradual recession of the aortic wave takes place throughout diastole. Correlation with the electrocardiogram (Fig. 4) shows that the QRS complex is completed a few hundredths of a second before the onset of ejection, as evidenced by the beginning aortic outthrust.



The end of the T-wave closely approximates the incisura, but the correlation is not precise, as it may either precede or follow it by 0.03 sec. in the same subject.

The aortic wave bears a striking resemblance to arterial pressure curves, and the changes in aortic volume represent, in fact, changes in lateral arterial pressure, although giving no information as to the absolute magnitude of the aortic pressure. It is really the same as a subelavian sphygmographic tracing which also records changes in arterial volume as a measure of pressure changes throughout the cycle,



Fig. 15.—Kymogram of a case of aortic insufficiency. Note the high peak of the second sound wave at the base of the diastolic limb of the ventricular wave and the primary collapse of the aortic wave.

but the kymogram possesses the advantage over the sphygmogram of being a direct and not an indirect method of registration.

The amplitude of the aortic wave, usually of the order of 0.5 cm., may thus be taken as a measure of lateral arterial pulse pressure provided that arterial elasticity is unchanged. The aortic wave provides a measure, in the same manner, of arterial elasticity, based on the excursion of the aortic wave per unit change in pressure, although quantitative application of this principle would first necessitate thorough standardization. A gross illustration of diminished arterial elasticity revealed in the aortic wave may, however, be seen in Fig. 16, No. 3,

where, despite a large pulse pressure associated with aortic insufficiency, the aortic wave is of very low amplitude. In this case there were sclerosis and calcification of the aortic arcus.

The waves of the ascending and descending aorta differ both in time relationships and in form. There is a measurable time delay between the beginning outthrust of the ascending and the descending arches of the aorta, averaging 0.03 sec., which is due to transmission of the pulse

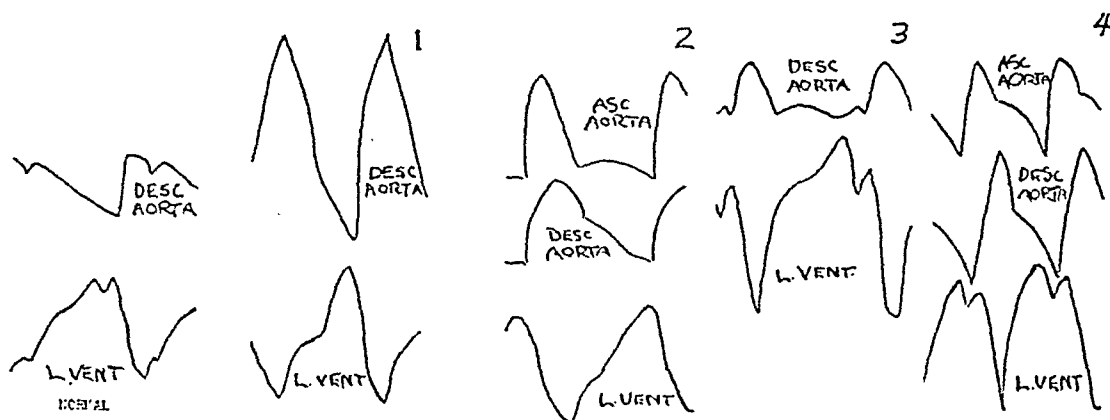


Fig. 16.—Ventricular and aortic waves in aortic insufficiency. These tracings reproduce the aortic and ventricular waves of several cases of aortic valvular disease. Definite changes in the aortic curve may take place in aortic insufficiency. The amplitude of the wave is greatly increased corresponding to the increase in pulse pressure. In contrast to the gradual retraction succeeding the peak, interrupted by a moderate incisural notch, which is seen in normal cases, the retraction succeeding the peak is greatly accentuated so that there is almost complete incisural collapse of the wave, and the aortic pressure is not sustained, being not much higher at the end than at the beginning of ejection. These changes are much more pronounced in the ascending than in the descending aorta. If the regurgitation is not severe the aortic wave approaches closely to normal. The amplitude of the ventricular waves are exaggerated in aortic insufficiency. This represents the increased systolic output of the left ventricle necessary in aortic insufficiency to maintain a normal circulating minute volume.

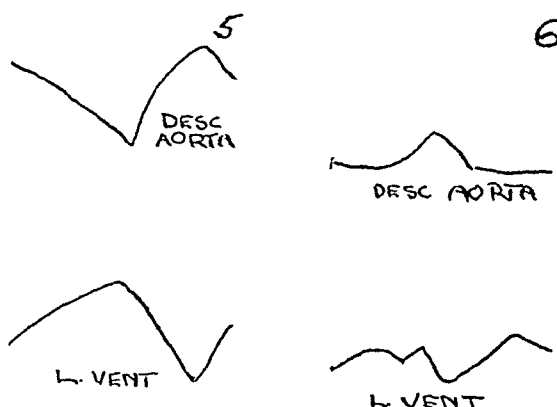


Fig. 17.—Tracing 5 shows the aortic and ventricular waves of a case of well-marked aortic stenosis (80/60). The waves are in striking contrast to those seen in aortic insufficiency. The outthrust of the aortic wave is very slow and gradual, with attainment of a late peak because of the reduced rate of ejection. The systolic limb of the ventricular wave likewise is slower than normal, and the amplitude of the ventricular wave is considerably less than in aortic insufficiency. These observations duplicate the findings in experimentally produced aortic stenosis using intravenous pressure curves.

wave. The distance between the two points of measurement is about 6 inches. This would give a velocity in the aorta of about 17 feet per second, which is of the same order of velocity as is found in determinations by subclavian and femoral sphygmograms. The range of error

over this short segment is so great, however, that at best only a crude indication of actual pulse wave velocity is obtained by this method.

Not only is there a time delay from the ascending to the descending aorta but the form of the wave changes. In the descending arch of the aorta the aortic pressure rises steeply with the onset of ejection, the rate or rise gradually diminishing with attainment of a peak at about midsystole. The curve then falls slowly with an appreciable retraction at the end of the ejection, which is halted by closure of the semilunar valves. In the ascending aorta the initial rise with the onset of ejection is much more abrupt and is practically linear. A sharp peak is attained within a few hundredths of a second in contrast to the blunted peak later in point of time in the descending aorta. The retraction succeeding the peak is much greater, but there is little rebound, so that the incisural notch is not usually as well marked.

Definite changes in the aortic curve may take place in aortic stenosis and insufficiency. In Figs. 16 and 17 are reproduced the aortic and ventricular waves of several cases of aortic valvular disease. In aortic insufficiency the amplitude of the wave is greatly increased, commensurate with the increase in pulse pressure. In contrast to the gradual retraction succeeding the peak, interrupted by a moderate incisural notch, as seen normally, the retraction succeeding the peak is greatly accentuated so that there is almost complete collapse of wave. The aortic pressure is not sustained, being not much higher at the end than at the beginning of ejection. These changes are much more pronounced in the ascending than in the descending aorta. If the regurgitation is not severe, the aortic wave approaches closely to normal.

Tracing 5 of Fig. 17 shows the aortic and ventricular waves of a case of well-marked aortic stenosis (blood pressure 80/60). The waves are in striking contrast to those seen in aortic insufficiency. The outthrust of the aortic wave is very slow and gradual, with attainment of a late peak because of the reduced rate of ejection. The systolic limb of the ventricular wave likewise is slower than normal, and the amplitude of the ventricular wave is considerably less than in aortic insufficiency. Katz, Ralli, and Cheer,<sup>5</sup> using intraventricular and aortic pressure curves, in experimentally produced aortic stenosis, have similarly demonstrated a reduced rate of systolic discharge.

The kymographic wave of the pulmonary artery is the only means available at present for recording the pulmonary arterial pulse wave. The wave resembles the aortic wave in all essential details. The incisura is more prominent than in the descending aorta.

Comparison of aortic and pulmonary arterial waves affords a method for studying asynchronism in the ejection phases of the two ventricles, the time of ejection being estimated from the beginning expansion of the vessel to the depth of the incisura. Because of the delay in transmission of the pulse wave from ascending to descending aorta, only the

ascending aorta can be compared with the pulmonary artery in recording the onset of ejection. Wolforth and Margolies<sup>18</sup> have recently similarly studied asynchronism in onset of ejection roentgenkymographically in bundle-branch block but recorded the aortic pulse at the aortic knob assuming a time delay of 0.010 to 0.015 sec. from the ascending aorta.

Table I shows the times of onset and duration of ejection of right and left ventricles in thirty normal individuals. It appears from these

TABLE I  
ASYNCHRONISM IN ONSET AND DURATION OF EJECTION OF LEFT AND RIGHT VENTRICLES, ESTIMATED FROM ASCENDING AORTIC AND PULMONARY ARTERIAL PULSE WAVES

	TIME OF ONSET OF EJECTION (SEC.) (FROM START OF RECORD)	DURATION OF EJECTION (SEC.)		TIME OF ONSET OF EJECTION (SEC.)	DURATION OF EJECTION (SEC.)
1. Aorta	0.28	0.24	16.	0.06	0.23
P. A.*	0.30	0.26		0.11	0.25
2. Aorta		0.21	17.	0.25	0.23
P. A.		0.24		0.29	0.21
3. Aorta		0.25	18.	0.34	0.23
P. A.		0.26		0.37	0.21
4. Aorta		0.22	19.	0.33	0.18
P. A.		0.26		0.33	0.19
5. Aorta	0.67	0.19	20.		0.27
P. A.	0.70	0.20			0.26
6. Aorta	0.54	0.20	21.	0.12	0.25
P. A.	0.57	0.23		0.15	0.23
7. Aorta	0.38	0.21	22.	0.52	0.21
P. A.	0.40	0.21		0.51	0.24
8. Aorta	0.18		23.	0.19	0.17
P. A.	0.22			0.22	0.18
9. Aorta	0.20	0.18	24.	0.66	0.19
P. A.	0.23	0.18		0.71	0.19
10. Aorta	0.29		25.	0.67	
P. A.	0.34			0.70	
11. Aorta	0.83		26.	0.48	0.22
P. A.	0.89			0.53	0.23
12. Aorta	0.92		27.	0.15	0.21
P. A.	0.94			0.21	0.25
13. Aorta	0.20	0.26	28.	0.16	
P. A.	0.22	0.24		0.21	
14. Aorta	0.43	0.25	29.	0.53	0.23
P. A.	0.47	0.24		0.55	0.27
15. Aorta	0.40	0.20	30.	0.56	0.18
P. A.	0.42	0.19		0.52	0.24

\*P. A., pulmonary artery.

records that neither the onset nor the duration of ejection of the two ventricles is necessarily simultaneous. The duration of ejection was the same in eleven out of twenty-four cases, within the limits of precision (0.02 sec.). In the remaining thirteen the duration of ejection was longer in the right ventricle in nine and in the left ventricle in four. In all four of these cases the left ventricle outlasted the right by 0.02 sec. The right ventricle outlasted the left by 0.02 sec. in two cases, 0.03 sec. in three cases, 0.04 sec. in three cases and 0.06 sec. in one case.

Katz,<sup>9</sup> in an experimental study of asynchronism in dogs, likewise found the right ventricular systole to outlast the left in the majority of cases. The range of variability in his series was 0.04 sec. for those cases of greater duration of left ventricular ejection and 0.07 sec. for cases with greater duration of right ventricular ejection.

In contrast, however, to the inconstant relation in precedence of ejection, reported by Katz, the kymographic studies would show that the onset of ejection regularly occurs earlier in the left than in the right ventricle. In none of twenty-eight cases analyzed did right ventricular ejection precede left, and in twenty-six the onset of ejection

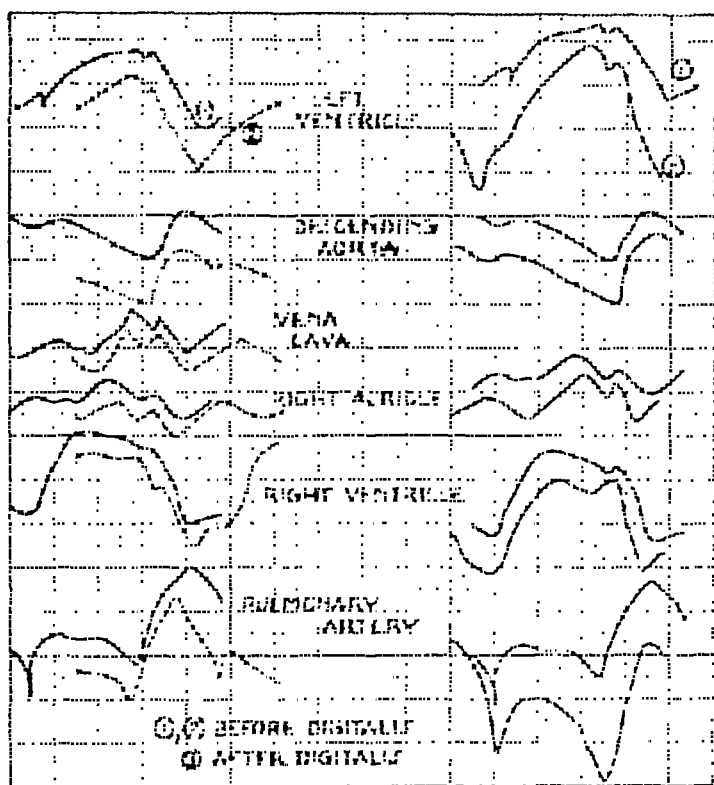


Fig. 18.—Kymographic waves in a normal heart before (1 and 2), and twenty-four hours after (3), digitalization. The waves at the left represent the movement of the various chambers before digitalis, in two examinations, one day apart, of the same subject. At the right, the lower wave (3) represents the movement of the chambers twenty-four hours after digitalis. Wave 1, the normal, is repeated for comparison.

occurred earlier in the left ventricle, ranging from 0.02 to 0.06 sec. and averaging 0.035 sec. If the onset of the contractile process is simultaneous in both ventricles, this priority of left ventricular ejection can only mean that the isometric, or presphygmie, period of systole is shorter for the left than for the right ventricle. Apparently the greater mass of left ventricular musculature more than compensates for the greater pressure that must be attained isometrically in the left ventricle before the opening of the semilunar valves and onset of ejection.

The effect of digitalization on the duration of ejection and the amplitude of motion of the kymographic waves in four normal hearts is summarized in Table II. No consistent effect was noted. Stewart and Cohn<sup>13</sup> found a reduction of 9 per cent in cardiac area, in investigating the effect of digitalis on normal hearts, and a decrease in systolic output, varying from 8 per cent to 30 per cent and averaging 20 per cent,

TABLE II

EFFECT OF DIGITALIS ON AMPLITUDE OF KYMOGRAPHIC WAVES AND ON DURATION OF EJECTION IN FOUR NORMAL HEARTS

	AMPLITUDE				DURATION OF EJECTION (SEC.)	
	L. VENT.	DESC. AORTA	R. VENT.	PUL. ARTERY	DESC. AORTA	PUL. ARTERY
	mm. $\times$ 4					
Bat.						
Control 1	5.3 mm.	15	12	14	0.24	0.27
Control 2	6.0	16	16	17	0.24	0.27
Digitalis—						
24 hr.	6.0	24	17	20	0.24	0.26
48 hr.	5.9	17	--	20	0.22	0.25
120 hr.	5.6	14	15	18	0.28	0.25
DeG.						
Control 1	4.5	10	11(?)	21	0.22	0.22
Control 2	4.5	10	12(?)	14	--	--
Digitalis—						
24 hr.	3.3	12	--	20	0.22	0.19
48 hr.	3.7	10	--	13	0.21	0.21
120 hr.	--	16	--	19	0.22	0.24
Rose						
Control 1	6.6	14	--	19	0.20	0.24
Control 2	5.5	14	14	--	--	--
Digitalis—						
24 hr.	6.9	16	16(?)	19	0.23	0.28
48 hr.	6.0	12	21	18	--	--
120 hr.	6.8	14	17	30(?)	0.23	0.27
Gre.						
Control 1	4.7	11	20	30	--	--
Control 2	4.7	12	24	24	0.26	0.38
Digitalis—						
24 hr.	5.8	16	22	32	--	0.32
48 hr.	5.8	14	21	26	--	(about) 0.36
120 hr.	6.1	14	20	27	0.27	0.27

determined by the acetylene method. The heart rate was slowed from four to fourteen beats. The maximum effects were obtained within twenty-four hours. Apparently these changes are not associated with any significant alteration in cardiac movement. Fig. 18 shows a graphic record of one of these cases. These tracings illustrate, also, the constancy of the kymographic waves in the same subject at different times.

## SUMMARY

Roentgenkymography records the movements of the heart and great vessels and is to be included among the methods of graphic registration of the cardiac cycle in man.

All the phenomena recorded kymographically conform readily to physiological interpretation, the information afforded by the ventricular, aortic, and auricular waves being the same as is obtained experimentally with the myocardiograph, arterial sphygmograms and jugular pulse tracings, respectively. On the basis of correlation with the electrocardiograms and heart sounds, the waves may be assigned to specific events in the cardiac cycle, and, by correlating these waves graphically, the sequence of events in the cardiac cycle may be accurately studied, with a time resolution of 0.02 sec.

The findings serve in the main to corroborate relationships determined by animal investigations. The kymographic method, in addition, sheds light on a number of interesting aspects of the cardiac cycle. Thus, it is the only method available for obtaining in man a graphic registration of occurrences in the pulmonary circuit.

Asynchronism in ejection of the two ventricles is studied by comparing aortic and pulmonary artery waves.

Physiological aortic regurgitation is demonstrated.

The changes in mitral and aortic valvular disease are shown, and a dynamic interpretation of these changes is given.

The effect of digitalization on the duration of ejection and movement is considered.

#### REFERENCES

1. Bardeen, C. R.: *Am. J. Anat.* 23: 423, 1918.
2. Eyster, J. A. E., and Meek, W. J.: *Am. J. Roentgenol.* 7: 471, 1920.
3. Henderson, Y.: *Am. J. Physiol.* 16: 325, 1906.
4. Hirsch, I. S.: *Radiology* 22: 403, 1934.
5. Hirsch, I. S.: *Radiology* 23: 720, 1934.
6. Hirsch, I. S.: *Brit. J. Radiol.* 7: 723, 1934.
7. Hirsch, I. S., and Schwarzschild, M.: *Acta Radiol.* 15: 101, 1934.
8. Katz, L. N., Ralli, E., and Cheer, S. N.: *J. Clin. Investigation* 5: 205, 1928.
9. Katz, L. N.: *Am. J. Physiol.* 72: 655, 1925.
10. Laurell, H.: *Upsala läkaref. förh.* 34: 495, 1928; 36: 133, 1931.
11. MacKenzie, Sir James: *The Study of the Pulse and the Movements of the Heart*, New York, 1902, The Macmillan Co., p. 197.
12. McCollum and McLure: Quoted by Wiggers,<sup>17</sup> *Physiology in Health and Disease*.
13. Stewart, H. J., and Cohn, A. E.: *J. Clin. Investigation* 11: 917, 1932.
14. Straub: (1917) Quoted by Wiggers,<sup>17</sup> *Physiology in Health and Disease*.
15. Sundberg, C. G.: *Acta Radiol.* 14: 558, 1933.
16. Tennant, R., and Wiggers, C. J.: *Am. J. Physiol.* 112: 351, 1935.
17. Wiggers, C. J.: *Physiology in Health and Disease*, Philadelphia, 1934, Lea & Febiger, p. 692.
18. Wolferth and Margolies: *AM. HEART J.* 10: 425, 1935.

# THE RELATIONSHIP OF TACHYCARDIA TO CARDIAC INSUFFICIENCY\*†

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IN EXPLAINING the common association of tachycardia with cardiac insufficiency, the acceleration usually has been regarded as a cause of the insufficiency. Although this explanation now is applied more especially to cases with auricular fibrillation, before recent data referring congestive heart failure to other causes became available, it was employed quite generally. Usually no particular explanation of the acceleration itself has been offered. Whether or not there is valid ground for the assumption that fast beating causes heart failure, however, there is indubitable evidence to show that myocardial failure is a prominent cause of acceleration.

## REFLEX ADJUSTMENT OF SINUS RATE TO OTHER FACTORS IN THE CIRCULATION

It is known that the various factors in the circulation tend to be maintained in proper balance by reflex adjustments. Primary change in ventricular rate tends to bring compensatory change in the systolic discharge and in blood pressure. Conversely, primary change in blood pressure, from variation in the arterial bed or in ventricular output, produces reciprocal effect in sinus rate.

Under the title, "Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease," Wiggers<sup>1</sup> says that "when arterial pressures fall, due to primary vasodilatation or to diminished cardiac output, the heart accelerates and strives to restore arterial pressures to normal." He reminds us of the pathways involved in this reflex acceleration, one over the afferent branches of the vagus from the root of the aorta, and the other through the so-called sinus nerve which is distributed solely to the carotid sinus, a reflex pathway exhaustively studied by Weiss and Baker.<sup>2</sup>

*Tachycardia in Peripheral Circulatory Insufficiency.*—It is beginning to be appreciated that this reflex mechanism is responsible for the tachycardia that usually accompanies failure of the peripheral circulation. In a recent publication Warfield<sup>3</sup> directs timely attention to this fact and reminds us that in such circumstances therapeutic effort must be

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directed not toward slowing the heart but toward improvement of the adverse factors in the peripheral circulation, of which tachycardia is but a physiological result.

*Tachycardia in Circulatory Insufficiency of Cardiac Origin.*—The same physiological response in heart rate is brought about also in cases of circulatory failure with normal rhythm in which the heart rather than the arterial bed is primarily at fault. The matter is expressed clearly by Wiggers:

The . . . compensatory type of cardiac acceleration is produced through these reflex mechanisms not only when peripheral vasodilatation exists but also when the systolic discharge of the heart is reduced. Shock and hemorrhage are two clinical conditions in which such a reduced output and compensatory acceleration obtain. But it is not so generally appreciated that the same reflex mechanisms operate when ventricular discharge is reduced as a result of myocardial failure and that the tachycardia which is so characteristically present is nature's only method of maintaining an effective circulation.

With the acceleration which nature institutes in a failing circulation, both phases of the cardiac cycle are shortened; and, as Lewis has emphasized, the lessening of the diastolic phase is proportionately greater than that of the phase of systole. The rest period is curtailed. Other circumstances also bear upon the work of the muscle. It receives less blood to expel. With each beat its work is less. Whether fast or slow, however, with each contraction it uses up its energy and then accumulates another supply. The term "cardiac reserve" applies not to a holding back in systole but to an ability to increase its use of available energy. One of its very means of putting its reserve capacity into use when called for is by acceleration—not a harmful but a useful process. With a rate too high for proper adjustment, diminution in output may embarrass the general circulation, but damage applies primarily not to the heart. This compensatory acceleration is described by Wiggers as follows:

Dynamic studies have shown that the faster the heart beats, the more the period of diastolic filling is cut short and the more the systolic discharge is decreased. However, calculations show that this decrease is more than compensated by the cardiac rate, up to 200 per minute, so that the minute output steadily becomes greater.

It is obvious that this compensatory acceleration must not be disturbed. To do so would cause a drop in blood pressure sufficient, perhaps, to endanger life itself. Fortunately there is no medicinal agent by which a compensatory sinus tachycardia can easily be abolished; otherwise many a patient with serious heart disease would have been helped prematurely to his grave through kindly intentioned but misguided treatment.

## HEART FAILURE AND THE THERAPEUTIC ACTION OF DIGITALIS

Wiggers' statement concerning misdirected attempts primarily to slow compensatory sinus tachycardia applies particularly to former notions of the harmful effects of acceleration upon the heart and to the use of digitalis primarily to reduce it.

More recent investigations relate heart failure not to the using of its available energy but to agents which impair the ability of the muscle to do that very thing. Infection, strain, and diminished blood supply particularly are involved. Such agents lessen the efficiency of the muscle by causing it to be less economical in transforming energy into work. It is now recognized that in congestive heart failure the efficiency of the ventricle is improved by the direct action of digitalis upon the muscle. Greater economy results. In a recent publication of great importance, Peters and Visscher<sup>9</sup> report their studies on "The Energy Metabolism of the Heart in Failure and the Influence of Drugs Upon It." They say:

Our main object in the study of the digitalis series of glucosides has been to determine whether they do or do not increase the efficiency with which the heart muscle is able to perform work. In every instance, among the clinically useful glucosides employed, there was an unmistakable increase in efficiency. . . . These drugs make the heart more economical in its utilization of energy and are therefore conservative in their effect.

*The Relationship of the Effect of Digitalis to Sinus Slowing.*—This therapeutic effect of digitalis directly upon the muscle of the ventricle, questioned by Mackenzie, was denied by Sir Thomas Lewis. Lewis insisted that the favorable action of the drug was to be attributed solely to its ability to reduce ventricular rate—a result obtained only in cases of auricular fibrillation. Sutherland and others, however, observing benefit in normal rhythm cases, administered the drug in normal rhythm also, with the object of slowing the rate.

Accumulated evidence that in congestive heart failure digitalis possesses a beneficial action unrelated to slowing finally became conclusive. It is known now that this action of the drug is exerted directly on the ventricular muscle. In normal rhythm cases, moreover, authorities now agree that improvement is due to this muscular action alone. They find that therapeutic doses produce little direct effect at the pacemaker but that, in cases with acceleration, slowing is an indirect effect which follows the improvement in the circulation produced by the action of digitalis upon the muscle of the ventricle.<sup>4, 5, 6, 7, 8</sup> With better circulation physiological mechanisms produce a reciprocal adaptation of rate. Tachycardia subsides. Just as acceleration results from impairment, so slowing results from improvement. Both are im-

portant indices of circulatory efficiency. Tachycardia may suggest that the circulation needs help; slowing indicates that appropriate measures have been effective.

In cardiac insufficiency with normal sinus rhythm, acceleration is not the cause of the failure; it is a physiological result. Primary slowing is not a proper therapeutic objective and is not a direct effect of digitalis. Improvement in muscular efficiency by digitalis or other agents results in subsequent slowing—a reflex adjustment in rate.

#### TACHYCARDIAS OF ABNORMAL RHYTHMS

With regard to abnormal rhythms it is evident that neither in origin nor in abatement do they represent compensatory adjustment of rate to other circulatory influences. Adaptation in other components of the circulation must be made, if possible, to meet the rate of the ectopic rhythm. As noted above, with sinus rates up to about 200 per minute, the circulation remains adequate, but in certain abnormal rhythms special factors obtain.

*A. Auricular Flutter.*—In auricular flutter the efficiency of the ventricular beat is lessened in some degree by the absence of auricular systole. Authorities differ somewhat regarding the extent of the circulatory impairment so produced. In the unusual instances of 1 to 1 ventricular response, the rate of the ventricle exceeds the upper limit at which compensatory adaptation in output can be accomplished. Blood pressure falls. The circulation is inadequate, and measures designed primarily to abolish the abnormal tachycardia may become in order.

*B. Independent Ventricular Rhythms.*—In ventricular tachycardia also the ventricle is deprived of the mechanical advantage of a preceding auricular systole. The rate usually is at about the upper limit at which adequate circulation can be maintained. In some cases the tachycardia itself thus may be a handicap, but a circumstance of much greater significance regularly obtains. The ectopic origin of the stimuli causes the muscular elements to be activated in abnormal sequence. The resulting contractions of the ventricular segments are much less efficient in expelling blood than is the concerted arrangement of normal systole. It is chiefly to this abnormal sequence of muscular contraction rather than to the high rate of beating or to the failure of auricular aid that circulatory insufficiency is to be attributed.<sup>1</sup> Primary efforts in such cases properly may be directed toward the restoration of normal rhythm.

*C. Auricular Fibrillation.*—In auricular fibrillation the excitatory impulses flow into the ventricular segments along normal paths; systole thus is spared the embarrassment that applies to independent ventricu-

lar rhythms. It is, however, deprived of the help normally supplied by auricular systole. In most clinical cases of fibrillation the minute rate of the ventricle is well below the critical physiological limit. But in many instances the fractional rate is too high, so that in cases with great acceleration the tachycardia itself may be somewhat disadvantageous with respect to optimum circulation. Certainly it would be desirable to abolish such an abnormal rhythm however slight might be its adverse circulatory effects, provided its cessation could be accomplished with reasonable prospect of permanence, and with minimum danger. The history of the disappointing use of quinidine in unselected cases of fibrillation need not be recited. In cases of heart failure with auricular fibrillation it is seldom possible to maintain normal rhythm by quinidine or other means.

As an alternative procedure, a proper reduction of ventricular rate in cases with excessive tachycardia obviously would be desirable for the general circulation. But in the average case with acceleration of lesser degree, less advantage would appear to accrue from primary reduction in rate, even if possible of accomplishment. For a long time, however, digitalis has been employed primarily with this objective. More recent information of the causes of heart failure and of the therapeutic action of the drug, and later data regarding the origin of fibrillation itself, now appear to necessitate a reexamination of this time-honored use of digitalis.

*The Origin of Auricular Fibrillation.*—Contrary to Lewis's dictum that persistent fibrillation means disease of the ventricular muscle, authorities now realize that no such interpretation is warranted.<sup>10, 11, 12</sup> In a recent study of 431 consecutive cases of the arrhythmia from the records of the Barnes Hospital, Dr. E. O. Jeffreys and I<sup>13</sup> found no suspicion of ventricular disease in forty-two cases. Auricular fibrillation is to be referred to the auricle. As precipitating factors, nervous influences and toxic agents have long been recognized. Later studies of the origin of clinical auricular fibrillation strongly suggest that in many instances a prominent precipitating factor is increase in intra-auricular pressure. In our series Dr. Jeffreys and I noted the usual findings, that mitral valve lesions were present in about one-third of the cases and that congestive heart failure was present in about two-thirds.

That stretching of the auricular wall from the increased pressure of congestive heart failure is a frequent factor in the origin of fibrillation is no new conception. It is supported by experimental data and by a rapidly increasing amount of clinical evidence. Congestive heart failure is so common a precipitating factor that, in any case in

which no other cause appears more probable, it should be suspected. In the excellent study recently made by Nahum and Hoff<sup>14</sup> those authors say:

When heart failure with auricular distention and venous engorgement occurs, the stretch of the auricle may contribute the necessary stimulus (E) which, when in association with vagus overactivity, precipitates auricular fibrillation. It thus becomes clear why this irregularity is so often associated with heart failure, being rightly regarded as an important evidence of the existence of heart failure.

All in all, in the average case of congestive failure and auricular fibrillation the probability increases that it is not the fibrillation which has caused the failure, but the failure which has caused the fibrillation. In many cases of heart failure observed over a period of time, the fibrillation is known to be secondary.

*Differentiation of Cases With Regard to the Slowing Effect of Digitalis.*—It is significant that in toxic cases of auricular fibrillation without heart failure, digitalis produces no slowing. In his classic treatise (1910), Mackenzie<sup>19</sup> said:

Moreover, when the heart is affected by agents which increase its excitability, the digitalis has little effect upon the rate, whether there is auricular fibrillation or whether the rhythm is normal. . . . This failure of effect is also evident in conditions where the heart is affected by poisons. . . . A modification in the susceptibility to digitalis is also produced by certain changes in the cardiac muscle.

Although the experience of physicians generally has made them aware of this fact, they appear more or less to have disregarded it.

Still another fact of perhaps greater import appears not to have been so generally appreciated. Not only in toxic cases but regularly in cases of fibrillation unassociated with heart failure, the therapeutic administration of digitalis is without slowing effect. We divided our cases on the basis of congestive heart failure. In the group without heart failure were put only cases in which there was no suspicion of failure. There were 97 in this group. In 47 of these cases without heart failure digitalis was administered, but in no instance did the record give evidence of a slowing effect on the pulse. It is possible, of course, that upon some occasion pulse records might have failed to reflect ventricular slowing, but it is extremely improbable that this could have obtained in many instances.

*Determination of Rate.*—In auricular fibrillation the ventricular rate is determined by the number of fibrillary impulses which evoke contractions of the muscle. Impulses which are not followed by contractions either fail to reach the ventricle, or, reaching it, find it unresponsive. In clinical explanations of any failure of ventricular response, it has been customary to give consideration to conductivity but to leave altogether out of account the matter of ventricular excita-

bility. Physiological investigation, however, finds the matter not so simple. Erlanger<sup>15</sup> holds that certain stimuli may reach the ventricle but find it unresponsive. He gives consideration to diminished excitability as an important factor in so-called A-V block. In normal rhythm, the P-R interval measures the time elapsing between the beginning of auricular activity and the recorded beginning of ventricular response. It cannot be regarded as a measurement of transmission time alone. The degree of ventricular excitability may be a factor as truly as the degree of conductivity. Sharp differentiation, in fact, between the ultimate fibers of the bundle and the rest of the musculature is impossible. They become an indistinguishable whole. Physiological evidence is to the effect that excitability and conductivity vary together.

It is known that as the ventricular rate falls irritability increases,<sup>16, 17, 18</sup> and that with improvement it diminishes again. Many years ago Cushny and his coworkers<sup>17</sup> took this fact into account in explaining the slowing effect of digitalis in cases of heart failure with fibrillation. In congestive failure digitalis appears to lessen both conductivity and irritability, if indeed they can be regarded as separate properties. At least it is known to lessen ventricular irritability,<sup>18</sup> which is more readily susceptible of separate measurement. It is significant that in fibrillation digitalis slowing occurs only in cases of heart failure, i.e., under circumstances in which muscular improvement regularly follows from the direct action of the drug, an effect which renders the muscle less susceptible to smaller fibrillary stimuli.

In explaining the block-producing effect of digitalis, attention has been centered too much on the A-V tissues, too little on the muscle of the ventricle. In the light of the demonstrated effect of the drug on the musculature, it appears illogical not to take this action prominently into account in explaining the lessening of ventricular response from digitalis in cases of auricular fibrillation with heart failure.

#### SUMMARY

The various elements of the circulation are subject to reflex variation. By reciprocal adjustments balance tends to be maintained despite disorder in one component.

Primary impairment of the peripheral circulation or of cardiac output produces reflex acceleration of sinus heart rate. Compensatory tachycardia is physiological, not harmful. Its primary abatement is not a proper therapeutic objective. Improvement is followed by reverse slowing. Conversely, primary acceleration of rate tends to induce compensatory adjustment in blood pressure, and in systolic discharge. With sinus rates nearly as high as 200, the circulation remains adequate.

Abnormal rhythms are not subject to reflex compensatory adjustment in rate. Certain special features, also, may affect the circulation adversely.

In auricular fibrillation the ventricular rate appears to depend largely upon the state of the ventricular muscle. This arrhythmia frequently occurs in congestive heart failure. Under such circumstances reduction in rate follows improvement in the muscle, from digitalis or from other cause. In cases of fibrillation without heart failure the muscular effect of digitalis is not beneficial; in such instances administration of the drug is not followed by slowing. In auricular fibrillation, as in normal rhythm, abatement of tachycardia appears not to be the cause of improvement but to be the result of it.

#### REFERENCES

1. Wiggers, Carl J.: Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease, *J. A. M. A.* 96: 603, 1931.
2. Weiss, Soma, and Baker, James P.: The Carotid Sinus Reflex in Health and Disease, *Medicine* 12: 297, 1933.
3. Warfield, Louis M.: Circulatory Failure, *J. A. M. A.* 106: 892, 1936.
4. Robinson, G. Canby: The Therapeutic Use of Digitalis, Baltimore, 1923, Williams & Wilkins Company.
5. Eggleston, Cary: Some Newer Concepts in Digitalis Therapy, *Am. J. M. Sc.* 160: 625, 1920.
6. Cohn, Alfred E.: Clinical and Electrocardiographic Studies on the Action of Digitalis, *J. A. M. A.* 65: 1527, 1915.
7. White, Paul Dudley: Heart Disease, New York, 1931, The Macmillan Company.
8. Marvin, H. M.: Digitalis and Diuretics in Heart Failure With Regular Rhythm With Especial Reference to the Importance of Etiological Classification of Heart Disease, *J. Clin. Investigation* 3: 521, 1927.
9. Peters, Howard C., and Visscher, Maurice B.: The Energy Metabolism of the Heart in Failure and the Influence of Drugs Upon It, *AM. HEART J.* 11: 273, 1936.
10. Fowler, W. M., and Baldrige, C. W.: Auricular Fibrillation as the Only Manifestation of Heart Disease, *AM. HEART J.* 6: 183, 1930.
11. Friedlander, Richard D., and Levine, Samuel A.: Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease, *New England J. Med.* 211: 624, 1934.
12. Orgain, Edward S., Wolff, Louis, and White, Paul D.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, *Arch. Int. Med.* 57: 493, 1936.
13. Luten, Drew, and Jeffreys, E. O.: The Clinical Significance of Auricular Fibrillation, *J. A. M. A.* (in press).
14. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methylcholine Chloride, With Observations on the Role of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* 105: 254, 1935.
15. Erlanger, J.: Irregularities of the Heart Resulting From Disturbed Conductivity, *Am. J. M. Sc.* 135: 797, 1908.
16. Cushny, Arthur R.: Digitalis and Its Allies, London, 1925, Longmans Green & Co.
17. Cushny, A. R., Marris, H. F., and Silverberg, M. D.: The Action of Digitalis in Therapeutics, *Heart* 4: 33, 1912.
18. Gold, Harry: Action of Digitalis in the Presence of Coronary Obstruction, *Arch. Int. Med.* 35: 482, 1925.
19. Mackenzie, J.: *Heart* 2: 273, 1910.

# THE DIFFERENTIAL DIAGNOSIS OF CONGESTIVE HEART FAILURE AND CONSTRICTIVE PERICARDITIS (PICK'S DISEASE)\*

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**I**N A symposium on cardiac insufficiency it seems appropriate that there be included a description of an important syndrome that produces a picture in many respects similar to that of congestive failure but in which the mechanism is entirely different and not dependent upon the failure of the heart as a pump. This syndrome is the one due to acute, subacute, and chronic constrictive pericarditis.

It is important that this be done for the reason that the therapy may be quite different from that of congestive failure and the prognosis, in suitable cases, is infinitely better. This lies in the fact that there is a specific treatment for many of these patients, namely, paracentesis in acute cases, and resection of the constricting pericardium in chronic cases, with marked or almost complete relief of symptoms in a large number.

In acute or subacute pericardial inflammation with more or less rapid accumulation of effusion, the effects on the circulation are the results of cardiac tamponade, the collection of fluid—serous, sanguineous, or purulent—compressing the heart and preventing its dilatation to receive the blood. In this syndrome all the signs may arise rapidly, and the patient appear to be suffering from marked peripheral venous distention and enlarged liver combined with the signs of much diminished cardiac output. The accumulated fluid may increase the cardiac dullness considerably, but cardiac tamponade becomes extreme only when the stretching of the pericardium is unable to compensate for the reduced diastolic volume of the heart. Such an event occurs in malignant or purulent pericarditis, either metastatic or from direct extension, in some cases of tuberculous effusion, rarely in rheumatic pericarditis, in cases of aneurysm rupturing into the pericardium, or rupture of the heart wall after coronary occlusion, and most characteristically in injuries to the heart from gunshot or stab wounds. In such cases the therapeutic indication is clearly not the reduction of the compensatory venous hypertension by venesection but the relief of the pressure on the heart by paracentesis of the pericardium or by surgical exploration

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and drainage. By repeated tapping some cases of inflammatory effusion may be helped to subside to such a stage of chronicity that pericardial resection may be feasible.

There still exists in the minds of many physicians the belief that the diagnosis of chronic constrictive pericarditis is almost impossible and that there is little to be gained from it except a sense of diagnostic satisfaction on the part of the doctor. This belief originates in a confusion between the various types of pericardial disease, some of which merely complicate the pathology of an otherwise badly diseased heart in which the discovery of a concomitant pericardial involvement has little bearing upon treatment or prognosis. This is true in the case of the commonest example of pericardial inflammation—that due to the pancarditis of rheumatic infection. In this condition the myocardium and the heart valves are, so far as we can prove, almost universally involved. In sixty-two cases of acute rheumatic pericarditis studied at the House of the Good Samaritan in Boston for periods up to ten years after the acute attack, there were only two cases which showed no clinical evidence of valvular deformity.<sup>1</sup> In such cases it is clear that the knowledge that an adherent pericardium exists, as assumed from the history of the acute attack, adds nothing to the therapeutic or prognostic implications except to reinforce the belief that a severe carditis has occurred, since rheumatic pericarditis, certainly as a part of pancarditis, does not cause Pick's disease so far as is attested by our experience. Furthermore, when patients with rheumatic heart disease suffer from congestive failure, the degree of this that is attributable to a complicating adherent pericardium cannot be differentiated from that due to the myocardial insufficiency. Completely adherent pericardium of itself is frequently an unimportant finding and is found in a considerable percentage of routine autopsies—2.26 per cent of the cases in a series of 1,900 autopsies from the Massachusetts General Hospital showed chronic pericarditis of some degree.<sup>1</sup> In most instances these pericardial scars and adhesions represent the historical mementoes of mild infections or perhaps the effects of the benign idiopathic pericarditis that not infrequently occurs and is probably not infrequently missed. It has not been proved that such infections, from which the patient apparently recovers completely, are ever the cause of constrictive pericarditis appearing in later life.

Pick's disease, on the other hand, is a condition that is usually progressive from the time of the original infection, and the inflamed pericardium in passing into a subacute stage or in healing gradually thickens as it enfolds the heart in its inelastic grip. Its etiology is unknown, but in our experience it would appear to arise from a tuberculous infection or from the agent responsible for respiratory infections, such as influenza and pneumonia. Rarely it follows septic pericarditis. Rheumatic infection has been outstandingly absent in our series.

## DIAGNOSIS

To arrive at a diagnosis of constrictive pericarditis it is necessary to be very critical of the evidences of congestive failure which are often grouped indiscriminately without reference to the vital distinction between right and left ventricular failure. In pure left ventricular failure the hypertension of the venous circuit predominates in the lungs, while in right ventricular failure it is most marked in the peripheral veins. Artificial as this rigid division may be in many cases of cardiac failure, it is fundamental in the diagnosis of all types of cardiac insufficiency. We may instance as pure left ventricular failure the syndrome of cardiac asthma and acute pulmonary edema in hypertensive heart disease, and as pure right ventricular failure the dilatation of the right heart following complete embolic obstruction of the pulmonary artery. But as a clinical picture in the terminal stages, hypertensive heart disease results in an added strain and hypertrophy of the right heart from the back pressure in the lungs and the development of peripheral edema and increased venous pressure. Similarly, so well marked an example of pure right ventricular failure as that seen in mitral stenosis occurs as a response to the hypertension in the lungs from the obstruction at the mitral valve so that there is increased venous pressure in both greater and lesser circuits.

These examples are what the "Criteria for the Classification and Diagnosis of Heart Disease," approved by the American Heart Association, describes as instances of cardiac insufficiency or "failure of the heart as a pump." This implies failure of the heart to empty itself in the sense of a force pump. In the case of Pick's disease there is primarily a failure of the heart to fill itself, or with the previous analogy, it can only be called "failure of the heart as a pump" if the heart is thought of as a suction pump. A rather similar condition actually exists in mitral stenosis in which the emphasis of venous engorgement presents itself in the pulmonary circuit due to inability of the left ventricle to fill properly through the stenosed mitral valve. Disregarding the eventual defeat of the right ventricle with its failure to empty, one sees a small left ventricle discharging into the aorta all that it receives, and it is no more to be blamed for the ineffectiveness of the arterial circulation than is the whole heart in Pick's disease.

By such analogies we arrive at the essential physiology of constrictive pericarditis in which the heart chambers are fundamentally normal but in which the blood is prevented from entering them either by adhesions about the exits of the venae cavae, or more often by the fact that the chambers are hindered in their capacity to dilate and receive the blood because of the inelastic armor of the thickened pericardium. In mitral stenosis the *vis a tergo* helping to force blood through the valve is the

power of the right ventricle, plus the pulmonic hypertension. In concretion cordis there is no mechanism to help fill the heart except the compensatory rise in peripheral venous pressure.

Naturally enough the syndrome of chronic constrictive pericarditis can be simulated by other obstructions to venous inflow of the heart, such as tumors, emboli, or thrombi in the venae cavae or right auricle, or by narrowing of the tricuspid valve. Since tricuspid stenosis is practically never seen without mitral stenosis, this does not enter into the differential diagnosis, provided mitral disease and its attendant pulmonary congestion are evident.

It follows, therefore, that the picture in Pick's disease is one of marked distention of the peripheral veins with either absent or only relatively slight distention of the pulmonic vessels, and the signs and symptoms are in accord. The chief points are these:

1. The patient is usually a child or young adult.
2. Ascites and enlarged liver appearing insidiously are always present and usually out of proportion to the peripheral edema.
3. The veins in the neck are engorged, and the venous pressure in arms and legs is often over three times normal. Moreover, the venous pressure remains constantly elevated, not fluctuating through periods of improvement or regression as it does in congestive heart failure. (The ascites alone may increase the femoral venous pressure considerably, and the pressure will be reduced somewhat by abdominal paracentesis.)
4. Dyspnea may be present to some degree on exertion, but orthopnea is strikingly absent when there is no pleural fluid.
5. Cyanosis consistent with venous engorgement is present and may be intense. When combined with lack of orthopnea and marked ascites, the inconsistency of these signs, at first suggesting congestive failure, is striking. Only marked tricuspid stenosis and pulmonary heart disease simulate it.
6. The heart size is normal in most cases—seven out of fifteen in the Massachusetts General Hospital series (moderate enlargement occurred in only three).<sup>2</sup>
7. The heart is free from murmurs except for infrequent apical systolic bruits. The rhythm is usually normal, but auricular fibrillation occurred in four of White's fifteen cases.
8. The blood pressure and pulse pressure are low. "Paradoxical pulse" was present in seven, absent in two, and not noted in six of the Massachusetts General Hospital series.
9. Broadbent's sign is absent.
10. Pleural effusions are common.
11. X-ray pictures of the heart may show calcification of the pericardium, limitation of cardiac pulsation, or limitation of pulsation of

the right border, dilatation of the superior vena cava, dilatation of the auricles, prominence of the left upper border, and pleural thickening. However, the examination may be essentially negative.

12. Electrocardiography shows low voltage in the axial leads, or inversion of the T-waves in Leads I and II, of the coronary type. One or both of these findings occurred in all of the fourteen Massachusetts General Hospital cases electrocardiographed.

13. The differential diagnoses of importance in our experience have been those of congestive heart failure (especially with mitral stenosis), cirrhosis of the liver, polyserositis, and nutritional edema.

#### SUMMARY

Acute and chronic constrictive pericarditis cause signs and symptoms suggestive of cardiac insufficiency (congestive failure) but should not be mistaken for it since paracentesis or the surgical relief of the chronic condition may result in complete disappearance of the patient's disability.

The diagnosis is made by noting, usually in a young person, the inconsistency between the finding of cyanosis, persistent venous distention, ascites, edema, and enlarged liver on one hand, and the absence of orthopnea, cardiac enlargement, and signs of valvular disease on the other. Helpful further evidence can be found in the low blood and pulse pressure, paradoxical pulse, limited cardiac excursion or calcification of the pericardium by x-ray, and low voltage or T-wave inversions in the electrocardiogram.

#### REFERENCES

1. Sprague, Howard B., Burch, Hobart A., and White, Paul D.: Adherent Pericardium and Pick's Syndrome. An Autopsy Study, *New England J. Med.* 207: 483, 1932.
2. White, Paul D.: Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, *Lancet* 2: 539 and 597, 1935.

## A CASE OF CONGENITAL AORTIC ATRESIA\*

WITH HYPOPLASIA OF ASCENDING AORTA, NORMAL ORIGIN OF CORONARY ARTERIES, LEFT VENTRICULAR HYPOPLASIA AND MITRAL STENOSIS

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**A**N EXTREME form of morbus ceruleus, which terminates fatally usually during the first few days of life, is associated with closure of the aortic or mitral valvular orifices. Cases of stenosis of these orifices, congenital or acquired, are not uncommon, but complete atresia of either passage is one of the very rarest types of congenital heart disease. Especially is this true of aortic atresia. The present case is accordingly reported, together with a survey of the previously described instances, which collectively point to the suggestion that the size of the interatrial aperture is a factor influencing the duration of life.†

### CASE REPORT

The subject was a colored male infant, the firstborn of twins. The mother (G. J.) was a negro girl, aged nineteen years, married one year, primigravida. She was first examined Oct. 30, 1934, when the last menstrual period was stated to have been in May, 1934. Wassermann test was negative. She was seen at intervals in the Charity Hospital Out-Patient Clinic until admission to the obstetrical ward of the Charity Hospital on January 14, 1935. No significant findings were discovered in her past or obstetrical history, or on physical examination. Pelvis of normal type. Fetal heart tones were heard to the left of the umbilicus, at a rate of 140 per minute. The first stage of labor began at 3:00 P.M., Jan. 14, 1935, the second stage at 4:30 A.M., Jan. 15, 1935, when the membranes were ruptured artificially. A frank breech, S. L. A., was delivered at 4:35 A.M.; the child breathed instantly and cried vigorously. At 4:50 A.M. the second child, vertex presentation, L. O. A., was delivered without difficulty; after two gasps this infant stopped breathing. Resuscitation was attempted for forty minutes, with the child taking occasional gasps at first; carbon dioxide, mouth-to-mouth breathing, alphalobelin, caffeine, contrast baths, and warmth all failed, and at 5:30 A.M. this second child was pronounced dead. Both were males. Their weights were, respectively, 6 pounds, 3 ounces, and 5 pounds, 6 ounces. The afterbirth was described as "one placenta, two cords, two sets of membranes."

The first child (the case here reported) died at the age of 20½ hours. When born he seemed to have neither cyanosis nor dyspnea, but very shortly thereafter cyanosis became apparent, and in the course of several hours there was also marked dyspnea. The cyanosis continued to deepen rapidly, and just before death both cyanosis and dyspnea were extreme.

*Autopsy.*—Negro male, body length, 47 cm. Second degree lividity of skin. Hair normal in amount and distribution. Nose showed a depressed bridge. Head

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†The writer is indebted to the Department of Pathology (Dr. Joseph Rigney D'Aunoy, director), the Charity Hospital of Louisiana, for the specimen here described.

showed loose suture lines, with evidence of craniotabes. Blood in mouth. Mesenteric vessels were somewhat engorged with blood, especially on the venous side. Lungs were almost completely atelectatic in the two upper lobes, and completely atelectatic in the three remaining lobes. They were about the color of liver, firm and rubbery in consistency. Very little crepitation was present. Liver weighed 105 gm. and capsule was tense; cut surface presented the appearance of a nutmeg liver. Spleen weighed 7 gm. and cut surface showed a little hyperemia and congestion. Kidneys

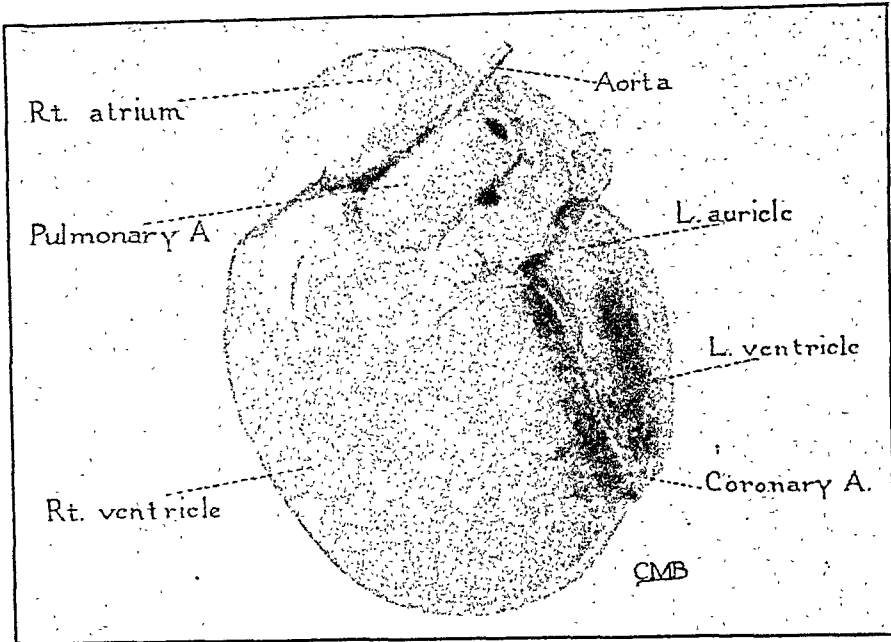


Fig. 1.—Anterior surface of heart.

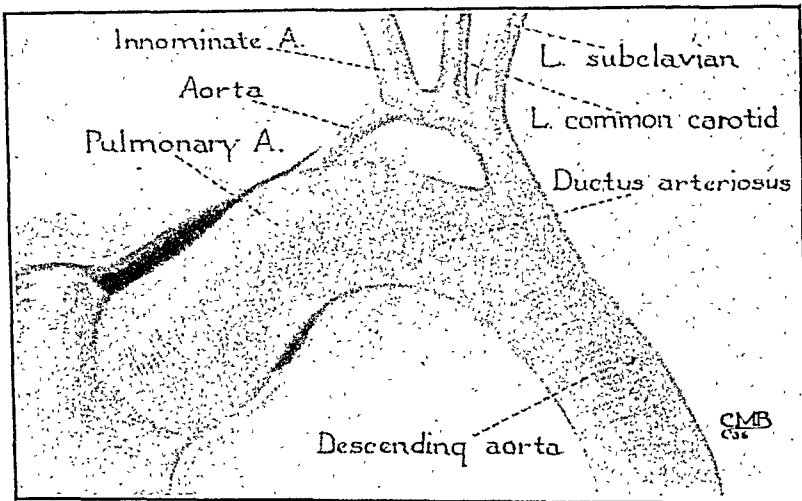


Fig. 2.—Vessels at base of heart, showing disproportion between pulmonary artery and aorta and manner by which blood from the ductus arteriosus reaches the ascending aorta, the vessels of the neck, and the descending aorta. (Functionally a "truncus solitarius pulmonalis.")

were congested, capsule tense, and cut edges everted on sectioning; they were red, with much uric acid deposition. Brain showed slightly engorged blood vessels. On sectioning, the epiphyses exhibited normal ossification centers and appeared perfectly normal.

*Microscopical Examination:* The *spleen* showed no increase in interstitial tissue, but the sinusoids were markedly engorged, and the pulp showed reduction in number of cells; corpuscles were numerous, small, but well defined. In the *liver* the

sinusoids of central portions of lobules were much engorged. Parenchymal cells in periphery of lobules showed rather marked fatty degeneration, and many islands of blood-forming tissue were found. In the *lung* the vessels were markedly engorged; a few of the alveoli were overdistended, but the majority were completely collapsed or only partially distended with air. *Kidney* except for congestion showed no morbid change. No other developmental abnormalities were seen except those of the heart, to be described in detail below.

*Anatomical Diagnosis.*—Congenital cardiac anomaly. Atelectasis of lungs. Marked congestion in liver, spleen, kidneys, brain and lungs.

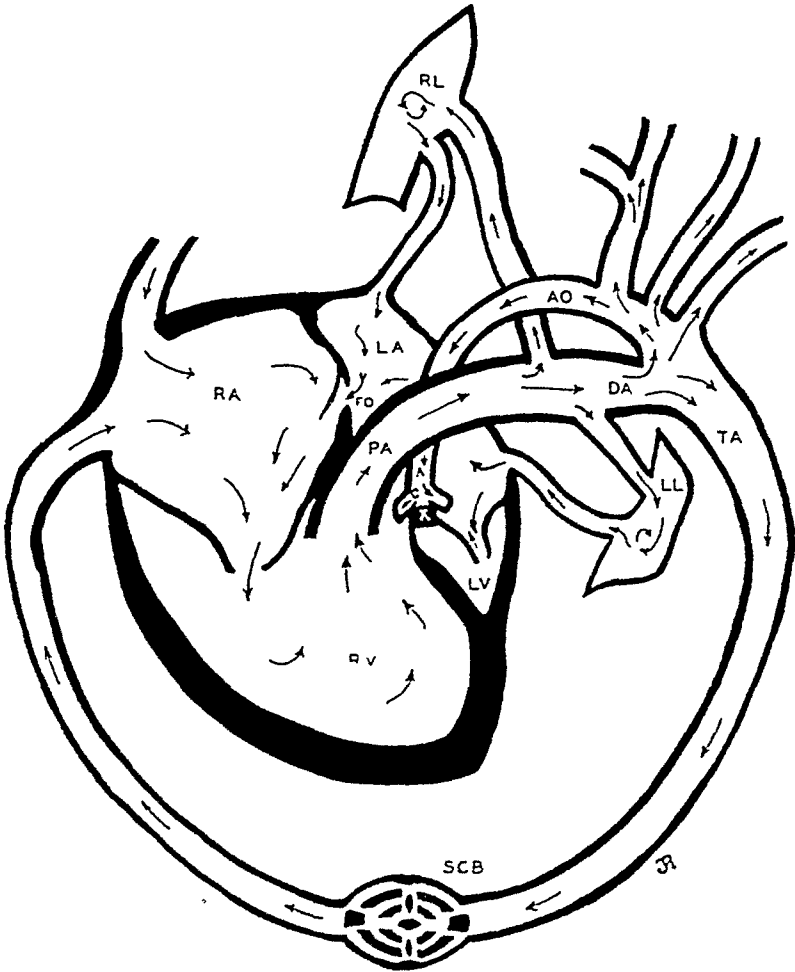


Fig. 3.—Diagram of the heart chambers and vessels, to show the probable course of the blood. (For clearness, no attempt is made to retain proportions here.) AO, arch of aorta; A, aorta ascendens; C, right and left coronary arteries; DA, ductus arteriosus; FO, foramen ovale; LA, left atrium; LL, left lung; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RL, right lung; RV, right ventricle; SCB, systemic capillary bed; TA, descending thoracic aorta; X, septum causing aortic atresia.

Autopsy on the second twin revealed nothing of significance except atelectasis of lungs and generalized passive congestion. The heart was normal.

#### *Description of Cardiac Anomaly*

The heart was approximately normal in general shape, in size (5.4 by 4.1 by 2.9 cm.), and in weight (25 gm.). It appeared well nourished, with no areas of infarction, ischemia, or anemia; the coronary vessels were engorged with blood, especially the veins. There was a great disproportion between right and left ventricles

(Fig. 1); the anterior width of the right ventricle was 3.2 cm., of the left, 0.9 cm. The apex was formed entirely by the right ventricle. The pulmonary artery was tremendously enlarged, being 13 mm. in external diameter at the root. The right and left branches of the pulmonary artery, superior and inferior venae cavae and pulmonary veins were normal. The ductus arteriosus continued in the direct axis of the pulmonary artery and was of the same diameter.

The aorta at once attracted attention. It was threadlike throughout its ascending and arched portions, being 2 mm. in external diameter. Near the isthmus it became slightly larger and gave origin normally to the three great vessels (Fig. 2). Below the isthmus the descending thoracic aorta was the expected diameter, appearing as the continuation of the large ductus arteriosus.

The right atrium was found to be greatly dilated and moderately hypertrophied. It measured 21 by 14 by 19 mm. and its walls were 1 mm. thick. The orifice of the coronary sinus was in its normal position, but much dilated. The right auricle was greatly dilated, appearing to be more directly a part of the atrial chamber than an appendage. On the septal wall was a very large fossa ovale which distinctly



Fig. 4.

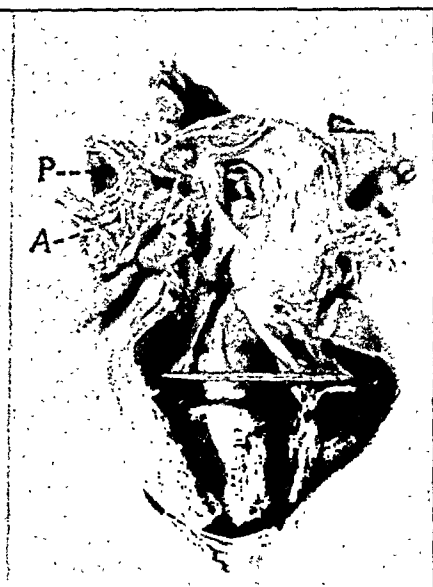


Fig. 5.

Fig. 4.—Heart opened to show enlargement of the right atrium and ventricle. Arrow indicates abnormal flap of tissue which prevents the flow of blood from right to left.

Fig. 5.—Heart opened to show marked hypoplasia of left atrium and ventricle. Note small opening of foramen ovale. A, ascending aorta; P, pulmonary artery.

bulged into the left atrium; it was circular, 11 mm. in diameter. The foramen ovale, 3 by 2 mm., was situated in the upper anterior portion of the fossa ovale. This was bounded in front by the prominent edge of the thick septum secundum (concave posteriorly) and behind by the edge of the thin, filmy septum primum. The foramen ovale so formed was in addition guarded by an unusual flaplike fold of tissue (Fig. 4); this bulged toward the right atrium, despite the "herniation" of the fossa ovale into the left atrium (Fig. 3). This fold or flap of tissue formed a valve which must have fairly effectively obstructed blood flow from right to left, while at the same time admitting it from left to right.

The tricuspid valve was 14 mm. in diameter; its cusps were normal in relative size and position although each cusp was actually much larger than usual. These cusps were attached as usual to three sets of large papillary muscles by rather massive chordae tendineae. The right ventricle showed marked dilatation and hypertrophy (Fig. 4). Its walls averaged 7 mm. thick, its internal width was



25 mm., depth 14 mm., and height 26 mm. The conus region was much larger than usual, appearing almost as an additional chamber; it opened into the pulmonary artery, which also showed extreme dilatation and hypertrophy. The pulmonary orifice, 9 mm. in diameter, was guarded by three strong, perfectly normal cusps which were in the usual positions. There was no opening in the aortopulmonary septum.

The left atrium (Fig. 5) was found to be less dilated than the right. Its walls were not hypertrophied, being less than 1 mm. thick. It measured 14 by 9 by 7 mm. The auricular appendage was in its usual position, but unlike that on the right was extremely hypoplastic; it joined the atrium by a narrow isthmus 1.5 mm. in diameter.

The left atrioventricular orifice presented a distinctly stenotic valve, tiny, funnel shaped, showing no subdivision into cusps. Its edges were connected by abnormally slender chordae tendineae to the left ventricular walls, with little evidence of papillary muscles. The valve was stenotic, the minimum diameter of the passage being less than 2 mm., while at the level of the fibrous ring it measured 6 mm.; evidently there existed a "mitral atresia" from a functional standpoint. The left ventricle, corresponding to the external indications of its size, was extremely hypoplastic. It was really little more than a slitlike cavity in the wall of the massive right ventricle, and it is thus easy to see why such a heart might be described as a

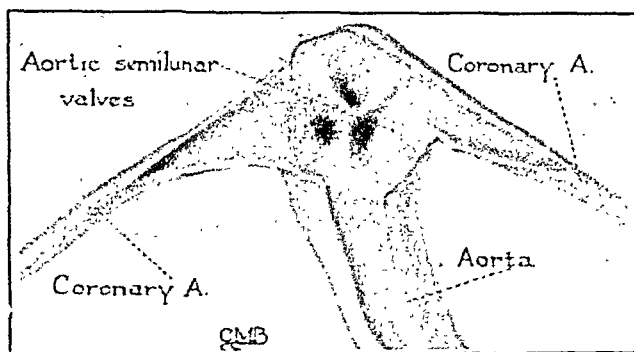


Fig. 6.—The opened aorta ascendens and two coronary arteries, showing the occluding septum which represents the fused semilunar cusps.

"cor pseudotriloculare biatriatum," as did Dolgopoli<sup>14</sup> in reporting her similar specimen. This cavity measured 2 mm. or less in width, 7 mm. in depth, 19 mm. in height, and would contain probably less than 0.5 c.c. No opening into the aorta could be found.

The interventricular septum was strong and well developed. It corresponded to the interventricular sulcus, which was displaced far to the left (Fig. 1). At the extreme upper part of the pars membranacea septi there was a shallow depression with an interventricular patency. However, this aperture was so small that only a 2 mm. probe could be passed through it into the pulmonic conus region; when passed from the right side, the probe entered the left ventricle just below the occluding aortic septum described below. Even this tiny patency was closed by a small tag of the septal cusp of the tricuspid valve which was attached to the upper edge of the septum by a thin chorda tendinea.

Although the arch and ascending part of the aorta admitted a thin wire, it could not be passed beyond the aortic ring. When the vessel was opened (Fig. 6), a complete occlusion, i.e., atresia, of the aortic valve was found. This was due to a transverse septum (X in Fig. 3), showing on its upper surface three shallow excavations separated by three low ridges which extended from the center of the septum 1.5 to 2 mm. along the aortic wall (Fig. 6). The septum represented the

fusion of the three semilunar cusps; the excavations, the sinuses of Valsalva; and the ridges, the lines of fusion of the cusps. The three little pits were of equal size, and corresponded in position to the normal cusps.

Arising from the right anterior and the left anterior excavations were the right and left coronary arteries. When opened, neither showed any union with the pulmonary artery or with any chamber of the heart. Their courses were normal in relation to the heart chambers.

*Microscopic Examination.*—Extreme thickening of endocardium, especially in left ventricle; atrophy of muscle fibers and replacement by dense fibrous connective tissue in left atrium and ventricle; congestion of vessels, especially near endocardium; no actual connections of vessels with the lumen of heart were found after detailed serial section study.

#### LITERATURE

The classical monographs on congenital heart disease dismiss aortic and mitral atresias with but a passing comment on their rarity and the associated extreme degree of morbus ceruleus. Many of the articles entitled "aortic atresia" are found to be descriptions not of real atresia but of stenosis of varying degrees. Aortic stenosis usually is not accompanied by the extreme cyanosis seen in atresia, nor is the prognosis so grave. In the following tabulation only those cases of true anatomical atresia are listed. A very careful search of the available literature and bibliographical aids revealed only fifteen cases of aortic atresia such as seen in this case. Some of these, however, differed in the associated cardiac anomalies.

Abbott<sup>1</sup> in her monumental collection of 850 cases of congenital heart disease found only six cases of aortic atresia.<sup>2-7</sup> In five of these there was an associated septal defect, and the foramen ovale and ductus arteriosus were nearly always widely patent. One of her cases was that reported by Summons<sup>2</sup>; his patient lived for fifteen weeks, which is by far the highest age attained by any reported case. Cyanosis and dyspnea were the prominent clinical features, as in all the cases.

Other instances apparently similar to the one here reported have been described by Philpott,<sup>8</sup> Bellet and Gouley,<sup>9</sup> Willer and Beck (two cases),<sup>10</sup> Farber and Hubbard,<sup>11</sup> and Wesson and Beaver.<sup>12</sup> Aortic atresia has been reported in two cases of cor biloculare (Hastings<sup>13</sup>; Konstantinowitsch<sup>3</sup>), in a case of transposition of aorta and pulmonary artery (Dolgopol<sup>14</sup>), and in three cases of cor triloculare biatriatum (Moore and Menne<sup>4</sup>; Dudzuz<sup>5</sup>; Shapiro<sup>15</sup>).

The case of Bellet and Gouley<sup>9</sup> is important because both the interatrial and interventricular septums were completely closed, and because of the "remarkable finding of numerous circular and oval channels in the left auricular appendage and left ventricle, some of which could be found by serial sections to communicate apparently with coronary arteries, through remains of the embryonic sinusoids. Thus it appeared that blood passed through them from the coronary arterioles to be delivered to the cavity of the left auricle and ventricle." [However, it

may be more likely that they served for passage of aerated blood from the left auricle and ventricle into the myocardium to aid in its nourishment.]

Farber and Hubbard<sup>11</sup> reached the conclusion that "fetal endomyocarditis was the cause of cardiac anomalies, especially in such cases as atresia or stenosis of valves." In fourteen collected cases of valvular stenosis or atresia (four being their own), they stated that "infection during fetal life seemed to be evident from gross and microscopic pathology." As in their instance of aortic atresia, in all these cases they found "enormous thickening of the endocardium (in the left ventricle), with hyaline degeneration in the muscle bundles, with abundance of finely divided fat droplets in the muscle fibers, and with definite calcification and cicatrization near the atresia." Three of their cases showing these changes were earlier reports of aortic atresia (Ruge<sup>6</sup>; Loeser<sup>7</sup>; Bellet and Gouley<sup>8</sup>).

Although partially descriptive, the titles of "truncus solitarius pulmonis" (Shapiro<sup>15</sup>) and "cor pseudotriloculare biatriatum" (Dolgop<sup>14</sup>) are quite misleading.

#### DISCUSSION

The size of the foramen ovale, and consequently the amount of blood that might pass through it, apparently were factors influencing the duration of life. All cases in which the duration of life and the size of the foramen ovale were mentioned have been arranged in a sequence according to the length of life (Table I). It is evident that the larger the foramen ovale, the longer the infant lived.

TABLE I

CASE*	LENGTH OF LIFE	SIZE OF FORAMEN OVALE	
	HOURS	MM.	REMARKS
1. Bellet and Gouley	12	--	"Completely closed."
2. This case	20	3 × 2	"Guarded by flap."
3. Loeser	40	--	"Open."
4. Willer and Beck, Case 1	43	4 × 3	"Small."
5. Wesson and Beaver	60	6.0	"Guarded by flap."
6. Philpott	62	9.0	"Widely patent."
7. Willer and Beck, Case 2	96	7 × 4	"Patent."
8. Shapiro	96	7.0	"Absent interventricular septum."
9. Dolgop	120	--	"Widely patent."
10. Hastings	144	--	"Absent interatrial and inter-ventricular septa."
11. Moore and Menne	144	--	"Relatively large patency."
12. Summons	2,520	--	"Extremely wide patency."

\*In Case 1, Farber and Hubbard,<sup>11</sup> the patient lived thirty-six hours, and the diagrams accompanying the protocol illustrate a foramen ovale patency of 4 to 6 mm., according to a personal communication from Dr. Farber.

The course of the blood was probably as follows (Fig. 3). Venous blood returning from the systemic circulation entered the right atrium. All of it passed into the right ventricle through the tricuspid orifice; its

entry into the left atrium was probably blocked by the flap guarding the foramen ovale. In the right atrium it was mixed with the small amount of aerated blood which could pass through the foramen ovale from left to right. From the right ventricle this mixed blood entered the pulmonary artery, then either the ductus arteriosus or the right or left pulmonary artery. Returned to the left atrium from the lungs, all or practically all the blood from this chamber reached the right atrium via the foramen ovale. Possibly a minute quantity of blood passed through the stenotic mitral orifice into the hypoplastic left ventricle, but having no outlet through the atretic aorta this would have been forced to return to the left atrium through the mitral valve. It is extremely doubtful that the minute interventricular patency would have admitted blood into the right ventricle, in view of its size and especially the presence of the guarding tag of the septal cusp mentioned above. Blood from the pulmonary artery entering the ductus arteriosus was continued into the descending thoracic aorta, or some of it might have entered the stenotic aortic arch in a retrograde direction, to be then distributed by its three branches, the innominate, left common carotid, and subclavian arteries.

Blood reached the coronary bed in the myocardium from one or more of the following sources: (1) From the ductus arteriosus, by passing through the arch of the aorta and down the stenosed ascending aorta to the coronary arteries; (2) from the lumen of the heart, through the Thebesian veins or the arterioluminal channels described by Wearn and his associates;<sup>16</sup> (3) from the lumen of the right atrium through the dilated coronary sinus and its tributaries, as suggested by the congested coronary veins; (4) from the extracardiac anastomoses described by Gross<sup>17</sup> and recently emphasized by Beck.<sup>18</sup> Probably the first source was most important.

The extreme cyanosis resulted from a combination of the "determining factors" of Lundsgaard and Van Slyke,<sup>19</sup> in the following order of importance: 1. The "alpha" factor (right-to-left shunt), for it is evident that very nearly all of the venous blood must have been shunted into the arterial stream through the large ductus arteriosus. 2. The "D" factor (increased reduction of oxygen in the tissue capillaries), produced by a retarded rate of flow as shown by the generalized passive congestion. 3. The "1" factor (lessened or retarded oxygenation in the alveoli of the lungs), due to the abnormal obstruction to the outflow of blood from the left atrium by the mitral and aortic closures and by the small foramen ovale, and resulting in the pulmonary congestion.

Theoretically, aortic atresia might be due either to a prenatal inflammatory condition which brought about adhesion of the valve cusps, or to an abnormal or arrested development at some critical stage of cardiac morphogenesis. This latter cause might be the evidence of hereditary deficiencies in germ cells or of a chemical, hydrodynamic, or pathological

condition in the environment interfering with normal development during the early weeks when the septums and heart were assuming form. In cases so arising there may be additional gross departures from normal, such as dextrocardia, large septal defects, transposition or persistent ostium atrioventriculare commune. In such cases,<sup>3, 4, 5, 13, 14, 15</sup> the aortic atresia would seem to be a secondary defect, possibly following an unequal division of the bulbus cordis by a displacement of the aortopulmonic septum; if so, the cusps would adhere to each other from contact and compression even in the complete absence of inflammation. Displacement of this septum might have been due to hydrodynamic abnormalities following initial displacement to the left of the atrial or ventricular septums, or to asymmetrical subdivision of the atrioventricular canal.

There is no conclusive evidence for the existence of fetal endomyocarditis due to intrauterine inflammatory conditions, except in syphilis. Histological examination was made, however, in eight<sup>6-12</sup> of the fifteen previously reported cases of aortic atresia and in the present case. In all nine, certain changes were found in the left ventricle (especially near the aortic ring) which suggested the effects of prenatal infection. These changes included: thickening of the endocardium, complete or partial obliteration of blood vessels, fibrous scars, overabundance of immature types of fibroblasts and fibers, general replacement of muscle fibers by dense fibrous connective tissue, atrophy of muscle fibers, hyaline or fatty degeneration of muscle fibers, and calcification or cicatrization near the atresia.

Of the other seven cases (in which microscopic study was not made), six<sup>3, 4, 5, 13, 14, 15</sup> showed associated grave anomalies suggesting that the cause was active very early in cardiogenesis, with the aortic atresia probably being a secondary defect. In the other case,<sup>2</sup> there were no data upon which to base either conclusion.

In no case was there evidence of syphilis; in cases in which a Wassermann test of baby or mother was mentioned (six cases), it was negative. Nine were males, three females; sex was not noted in four. Color was not stated in seven; seven were white and two negro. The ages of the mothers (given in six cases) averaged nineteen and one-half years; the oldest was twenty-four years. Two of the patients were twins.

#### SUMMARY

The case reported here is the tenth showing aortic atresia associated with the usual combination of defects (mitral stenosis, left ventricular hypoplasia, stenosis of ascending aorta and arch, patent foramen ovale, right ventricular and pulmonary artery dilatation and hypertrophy, enlarged ductus arteriosus, and nonpatent interventricular septum). Six additional cases in the literature show grave congenital defects (absent

septums; transposition of aorta) associated with aortic atresia, making this the sixteenth recorded case of congenital aortic valvular atresia.

The probable course of the blood is suggested, especially for the coronary circulation.

All cases which have been studied histologically indicate that there might possibly have been a prenatal inflammatory condition; the alternate theory of arrested development is also discussed.

The size of the interatrial aperture or foramen ovale is shown to be a factor probably influencing the duration of life in cases of congenital aortic atresia.

It is a pleasure to acknowledge my appreciation to Dr. Harold Cummins, professor of microscopic anatomy, and to Dr. John H. Musser, professor of medicine, of the Tulane University, who read the manuscript.

#### REFERENCES

1. Abbott, M. E.: Congenital Heart Disease: Monograph in Osler-McCrae, *Modern Medicine* 4: 612, 1927.
2. Summons,\* W. F.: Congenital Heart Disease, *Intercolonial M. J. of Australasia* 11: 65, 1906.
3. Konstantinowitsch: Quoted by Abbott.<sup>1</sup>
4. Moore, C. U., and Menne, F. R.: Report of Case of Congenital Anomaly of Heart—Reptilian, *Heart* 8: 297, 1921.
5. Dudzuz, M.: Ueber Cor Triloculare Biatrimum mit Atresie des linken venösen Ostiums, *Virchows Arch. f. path. Anat.* 237: 32, 1922.
6. Ruge, K.: Ueber angeborene Herzfehler mit besonderer Berücksichtigung der entzündlichen Stenose und Atresie der Aorta, *Diss., Kiel*, 1905. Quoted by Farber and Hubbard.<sup>11</sup>
7. Loeser, A.: Ueber kongenitale Aortenstenose und fötale Endocarditis, *Virchows Arch. f. path. Anat.* 219: 309, 1915.
8. Philpott, N.: Congenital Atresia of Aortic Ring, *Ann. Int. Med.* 2: 422, 1928.
9. Bellet, S., and Gouley, B. A.: Congenital Heart Disease, With Multiple Cardiac Anomalies: Case Showing Aortic Atresia, Fibrous Scar in Myocardium and Embryonal Sinusoidal Remains, *Am. J. M. Sc.* 183: 458, 1932.
10. Willer, H., and Beck, L.: Congenital Stenosis of Aorta Ascendens With Atresia of Aortic Orifice; Two Cases, *Ztschr. f. Kreislaufforsch.* 24: 633, 1932.
11. Farber, S., and Hubbard, J.: Fetal Endo-myocarditis; Intrauterine Infection as the Cause of Congenital Cardiac Anomalies, *Am. J. M. Sc.* 186: 705, 1933.
12. Wesson, H. R., and Beaver, D. C.: Congenital Atresia of Aortic Orifice, Stenosis of Ascending Aorta, Patent Foramen Ovale, Persistent Ductus Arteriosus, Ventricular Septum Entire, and Rudimentary Left Ventricle, *J. Tech. Methods* 14: 86, 1935.
13. Hastings, W. S.: A Case of Cor Biloculare With Atresia of Aorta, *J. Tech. Methods* 10: 194, 1929.
14. Dolgopel, V. B.: Cor Pseudo-Triloculare With Atresia of Mitral and Aortic Ostia, *J. Tech. Methods* 13: 100, 1934.
15. Shapiro, P. F.: Truncus Solitarius Pulmonis, *Arch. Path.* 10: 671, 1930.
16. Wearn, J. T., Mettler, S. R., Klumpp, T. H., and Zschiesche, L. J.: The Nature of Vascular Communications Between the Coronary Arteries and the Chambers of the Heart, *AM. HEART J.* 9: 143, 1933.
17. Gross, L.: *The Blood Supply of the Heart*, New York, 1921, Paul B. Hoeber.
18. Beck, C. S., and Tiehey, V. L.: The Production of a Collateral Circulation to the Heart, *AM. HEART J.* 10: 849, 1935.
19. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine* 2: 1, 1923.

\*Name often misspelled "Simmons."

## SUDDEN ARTERIAL OCCLUSION IN THROMBOANGIITIS OBLITERANS\*

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**I**T IS not surprising that occlusion of the main arteries may occur suddenly in thromboangiitis obliterans. In sclerosis of coronary arteries, which is a chronic occlusive arterial disease of a different type from that observed in thromboangiitis obliterans, sudden occlusion of the coronary arteries, which is recognized as thrombosis of the coronary arteries and myocardial infarction, occurs frequently. Sudden arterial occlusion in thromboangiitis obliterans has been emphasized in the monograph of Buerger, in the monograph of Brown, Allen, and Mahorner, and by Barker. Brown, Allen, and Mahorner said that "sudden arterial occlusion is usually indicated by sharp pain in the foot. Inspection shows extreme pallor and coldness of the extremity. Pain subsides gradually and usually disappears in from twenty-four to seventy-two hours. The pallor partially disappears and in the ends of the toes is replaced by excessive rubor or cyanosis. Claudication and other symptoms of thromboangiitis obliterans may follow shortly or be delayed for months. So frequently is this syndrome present that we make a tentative diagnosis of thromboangiitis obliterans in all cases of sudden unexplained occlusion of the peripheral arteries occurring in young adult males." Of sudden arterial occlusion, as an initial symptom, they said that "occasionally the first symptoms in thromboangiitis obliterans are those due to sudden arterial occlusion, consisting of the sudden onset of pain followed by pallor and coldness of the extremities. Some color and warmth usually return after prolonged rest, but mild pain on rest and claudication are the usual sequelae."

It is the purpose of this study to determine how frequently sudden arterial occlusion occurs in thromboangiitis obliterans, both as an initial event and as an episode in the course of well established thromboangiitis obliterans, to delineate the symptoms of this condition, and to study the events subsequent to it. For these purposes the records of 255 carefully studied cases of thromboangiitis obliterans were examined.

### SUDDEN ARTERIAL OCCLUSION IN THE COURSE OF ESTABLISHED THROMBOANGIITIS OBLITERANS

This group consisted of fifteen cases, or about 6 per cent of all the cases which were studied. It is probable that the percentage incidence of sudden arterial occlusion in the course of thromboangiitis obliterans noted is low, as only characteristic incidences of this complication were

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included in the group. Were it possible to have a large number of patients with thromboangiitis obliterans under personal observation for a long time, it is probable that sudden arterial occlusion would be found to occur in somewhat more than 6 per cent of the cases. Sudden occlusion could be determined then, not only on the basis of symptoms, as was necessary in this study, but on the basis of sudden disappearance of pulsations in the peripheral arteries.

There can be no reasonable doubt regarding the diagnosis of thromboangiitis obliterans in any of these cases. All of the patients were men, except the patient in Case 15, who was a woman. The early details of this case have been reported previously as Case 16, by Horton and Brown. Chronic occlusive arterial disease is clearly indicated in each instance by symptoms of this condition, such as intermittent claudication, and by previous examination in many instances. The patients were all young or middle-aged individuals at the time symptoms of vascular disease were first noted, with the exception of the patients in Cases 5, 7, and 14. In each of these cases there was predominant evidence of an inflammatory type of arterial lesion rather than a degenerative one, although arteriosclerosis as a basis for arterial occlusion could not be entirely excluded.

It is apparent from this study that the time which elapsed between the onset of the disease and the appearance of sudden arterial occlusion varied within wide boundaries. One patient had had evidence of thromboangiitis obliterans for sixteen years before there was rapid interference with the arterial circulation; another one had had intermittent claudication for only three months previously (Table I). Symptoms likewise varied widely, from a sudden decrease in surface temperature to severe pain. This observation agrees with that of McKechnie and Allen; namely, that symptoms of sudden arterial occlusion not associated with chronic occlusive arterial disease are characterized by severe pain in only about half of the cases; in the remaining 50 per cent of cases, numbness, tingling, and coldness were predominant symptoms. As McKechnie and Allen have stressed in their previous study, the diagnosis of sudden arterial occlusion is not dependent on the accepted classic symptom of sudden severe pain in an extremity.

Sudden occlusion of arteries in thromboangiitis obliterans appears to be a serious complication as in ten, 66 per cent, of the fifteen cases it was eventually necessary to amputate the limb in which sudden occlusion had occurred. This is an extremely high incidence of amputation in thromboangiitis obliterans of all types, and exceeds the incidence of this operation in arterial embolism and thrombosis, which are not associated with chronic occlusive arterial disease, as the study of McKechnie and Allen showed that amputation is necessary in only about half of such cases. The explanation for the high incidence of amputation seems to be that extremities in which the arterial blood supply is already greatly reduced



TABLE I

## SUDDEN ARTERIAL OCCLUSION IN ESTABLISHED THROMBOANGITIS OBLITERANS

CASE	AGE IN YR.	SYMPTOMS		TIME OF SUDDEN OCCLUSION*	RESULTS OF SUDDEN ARTERIAL OCCLUSION
		BEFORE SUDDEN OCCLUSION	OF SUDDEN OCCLUSION		
1	44	Claudication for five years	Sudden pain	Three years	Amputation†
2	29	Claudication for one and a half years. Phlebitis	Sudden numbness and coldness; partial paralysis	Seven months	Ischemic neuritis; amputation eight months after acute occlusion
3	57	Bilateral claudication of feet for sixteen years. Right second toe had been amputated	Coldness and pain	Eighteen days	Claudication in right calf; rest pain relieved by treatment
4	37	Claudication of right calf, and later amputation of right leg	Coldness and redness of toes	Three weeks	Temporary recovery; leg amputated later
5	54	Claudication for three months	Sudden severe pain, and pallor and numbness	Nine weeks	Amputation; claudication developed later and there was occlusion of arteries of remaining leg
6	37	Claudication for one year	Sudden sensation of numbness and "deadness"	Three years	Temporary recovery; eventual amputation
7	51	Claudication for two years	Severe pain and coldness; numbness and partial paralysis	Three days	Amputation in one month
8	38	Claudication for ten years. Superficial phlebitis	Sudden discoloration and coldness of left foot	Eight months	Temporary recovery; amputation eight months after sudden occlusion
9	49	Claudication left arch and calf for two years	Sudden numbness and coldness of foot	Three weeks	Recovery from acute symptoms
10	44	Claudication. Amputation of left leg	Severe pain, cyanosis of toe nails, and anesthesia of distal half of foot	‡	Ischemic neuritis; gradual recovery; amputation in three months†
11	46	Claudication for one year	Sudden cramp in left foot	Three months	Recovery from acute symptoms in two days
12	28	Claudication for three years	Sudden onset of numbness, pallor and coldness of left leg	Three days	Residual ischemic neuritis which improved; amputation eighteen months later

\*Before examination at the clinic.

†Elsewhere.

‡Sudden occlusion occurred while patient was under our care.

TABLE I—CONT'D

CASE	AGE IN YR.	SYMPTOMS		TIME OF SUDDEN OCCLUSION*	RESULTS OF SUDDEN ARTERIAL OCCLUSION
		BEFORE SUDDEN OCCLUSION	OF SUDDEN OCCLUSION		
13	35	Amputation of right leg	Numbness, cold- ness and dis- coloration of left foot	Three weeks	Recovery from acute symptoms
14	53	Claudication for two years	Pallor, coldness and pain affect- ing left foot and leg	Three days	Gangrene and amputation
15	30	Claudication	Sudden decrease in temperature of foot	†	Recovery

cannot survive further sudden reduction in blood supply for long. It also is probable that cases in which sudden arterial occlusion occurs are representative of a more progressive form of thromboangiitis obliterans. Only two of these patients were under our observation at the time the blood supply to the extremity was suddenly diminished; the others were examined and treated at intervals ranging from three days to three years after the sudden thrombosis. Had all these patients received the very best of care immediately after thrombosis occurred suddenly, it is probable that amputation would not have been necessary so frequently. This, however, is by no means an absolute certainty.

#### SUDDEN ARTERIAL OCCLUSION AS AN INITIAL EVENT IN THROMBOANGITIS OBLITERANS

There were eleven cases in this group, or about 4 per cent of the entire group studied. It is a fair assumption that the diagnosis of thromboangiitis obliterans is established when bilateral occlusive arterial disease of a progressive nature affects young men, when the onset of some of the occlusive lesions is gradual. In addition to bilateral arterial occlusion, no cardiac lesions were detectable which might be sources of embolism. Additional support for the diagnosis of thromboangiitis obliterans was the occurrence of superficial phlebitis in Cases 3 and 10, the gross and microscopic studies of the arteries in Cases 2 and 11, and the characteristic arteriogram in Case 9 (Table II). In all of the cases except Cases 9 and 10, the lesions affected the legs. All of the patients were men. In Cases 6 and 11 the occlusive lesion was unilateral at the time the patient first was examined at the clinic. In both cases, the diagnosis of thromboangiitis obliterans was made primarily, and subsequently was substantiated by the appearance of bilateral occlusion of arteries. In Case 11, the diagnosis was proved by microscopic examination of the arteries. Cases 2 and 11 were the only cases in which subsequent amputation was necessary. In Case 2 amputation was performed nine years after sudden arterial occlusion had occurred. In Case 11, the thrombo-

TABLE II

## ONSET OF THROMBOANGITIS OBLITERANS WITH SUDDEN ARTERIAL OCCLUSION

CASE	AGE IN YR.	SYMPTOMS		PROOF OF THROMBO-ANGITIS OBLITERANS
		OF SUDDEN ARTERIAL OCCLUSION	SUBSEQUENT TO ACUTE OCCLUSION	
1	48	Sudden pain in left calf	None for one and a half years, claudication then appeared	Bilateral arterial occlusion
2*	39	Severe pain in right ankle and calf; leg pale; pain persisted two weeks	Claudication, ischemic neuritis, and gangrene after nine years; amputation	Bilateral amputation of legs; gross and microscopic examination of arteries
3	50	Sudden severe pain; numbness and immobility of right leg	Claudication	Phlebitis; bilateral arterial occlusion
4	45	Sudden pain in left calf and posterior thigh, and numbness of foot	Unknown	Bilateral arterial occlusion
5	39	Sudden severe pain in left leg, which lasted ten days	Claudication; gangrene of toes three years later	Bilateral arterial occlusion
6	42	Sudden pain in right calf	Claudication	Bilateral arterial occlusion†
7	36	Sudden numbness, coldness, and pallor of left leg	Claudication	Bilateral arterial occlusion
8	30	Numbness of left foot	Claudication	Bilateral arterial occlusion
9	37	Sudden numbness and coldness in left second finger, followed by ulceration	None	Claudication in legs two years later; arteriogram
10	39	Sudden pain and swelling of second, third, fourth, and fifth fingers of right hand	None after three months	Superficial phlebitis; bilateral arterial occlusion
11	40	Sudden severe pain in right mid thigh; ten days later, same type pain in right calf; leg cold and white	Pain replaced by claudication in two weeks; ulceration of right great toe appeared three months later; amputation of right leg two months later	Bilateral occlusive arterial disease; microscopic examination of arteries
		Sudden severe pain, numbness and coldness of left leg, associated with disappearance of pulsations in femoral artery	Gangrene; amputation necessary	Microscopic examination of arteries; bilateral arterial occlusion†

\*Patient had had symptoms in left leg and right hand five years before amputation of left leg, which was performed five years after onset of symptoms.

†At time of first examination arterial occlusion was unilateral.

angiitis was of a particularly malignant type, and it was necessary to amputate the left leg two weeks after sudden arterial occlusion had occurred, and it was necessary to amputate the right leg six months after the occurrence of sudden arterial occlusion. This patient was the only one of this group who was under our observation at the time of sudden thrombosis. The periods of known survival of limbs in cases in which amputation was not necessary following sudden occlusion of arteries were two and a half years (Case 1), six years (Case 3), fifteen days (Case 4), four years (Case 5), two years (Case 6), one year (Case 7), four years (Case 8), two years (Case 9), and twenty months (Case 10). It is apparent that the periods of survival of the affected limbs are considerably greater than those indicated, as many of these patients would have returned to the clinic for reexamination if further serious trouble had occurred. In Case 2 amputation was performed nine years after sudden occlusion had occurred, and this surgical procedure was hardly necessitated by sudden occlusion. In only one case (Case 11), or 9 per cent of Group 1, did the necessity for amputation eventuate soon after sudden arterial occlusion. When contrasted with the 66 per cent of amputations which eventually were necessary in the group of cases in which there was clinical evidence of thromboangiitis obliterans before sudden occlusion occurred, the number of amputations is remarkably small. The explanation seems obvious; when sudden arterial occlusion occurs in the presence of an already diminished blood supply, the consequences are much graver than when the arterial circulation is approximately normal. Intermittent claudication resulted in all cases except Cases 4, 9, 10, and 11. In Case 4 the information was not available. In Cases 9 and 10 the lesion affected the arms, and the second sudden occlusion in Case 11 resulted in gangrene, and amputation was necessary shortly afterward.

#### TREATMENT

Prompt recognition and treatment of sudden arterial thrombosis is important. It is probable that very little of value can be accomplished if twenty-four to forty-eight hours elapse before rational treatment is begun. Undoubtedly, other circumstances being equal, the prospects of a satisfactory recovery are proportional to the promptness with which logical treatment is instituted. Treatment of this complication is one which cannot be delegated judiciously to nurses or relatives, but warrants the almost constant attention of a physician until the circulation is reestablished, or until an unfortunate outcome is apparent.

There are three aims in the treatment of sudden arterial occlusion: (1) to relieve pain; (2) to avoid doing harm to the extremity, which has an impoverished blood supply; and (3) to induce as much vasodilatation as possible. Administration of morphine is advisable for the relief of pain. As in myocardial infarction, which is the result of thrombosis of a coronary artery, administration of large amounts of morphine may be

necessary, but the patient should be made comfortable. The placing of hot water bottles around the extremity is dangerous, as serious burns may result because the blood supply is greatly diminished and the tissues are very sensitive to temperatures which ordinarily are harmless. As a substitute for this time-honored method, we recommend wrapping the limb with absorbent cotton, which is held in place with an ordinary roller bandage. A cradle which contains electric light bulbs should be placed over the affected limb and covered with a sheet. The temperature within the cradle should not exceed 100° F., and a temperature of about 90° F., probably is advisable. The affected limb should be placed definitely below the level of the heart.

The outcome of sudden thrombosis of an important artery depends on the ability of arteries, which ordinarily are of secondary importance, to assume a heightened function of transmission of blood, that is, to undergo vasodilatation, since the occluded artery has become functionless by virtue of the thrombosis. The experimental work of Mulvihill and Harvey has demonstrated conclusively that the decrease in the circulation which follows arterial ligation can be offset completely by sympathectomy, which we assume either relieves actual spasm of collateral arteries or induces them to accept an increased function in contrast to that which they have normally. These observations are supported clinically by the encouraging report of Herrmann and Reid, who used an alternating positive and negative pressure (pavacx method) around the affected limb, and by the reports of Denk and of Allen and MacLean, who injected papaverine intravenously. Both of these therapeutic procedures produce a common effect, that is, arterial dilatation. In addition, vasodilatation can be effected in varying degrees by the oral administration of alcohol, as has been shown by Cook and Brown, or by the oral or intravenous administration of theobromine, as has been shown by Newell and Allen, and by Seupham or by the administration of acetyl-beta-methylcholine as has been shown by Goldsmith. Ethyl alcohol can be administered orally in orange juice or ginger ale, in doses of about 0.5 c.c. for each kilogram of body weight. The vasodilating effect of theobromine probably is too weak to be of use in sudden arterial occlusion, but the drug may be given by mouth in doses of 20 grains (1.3 gm.).<sup>14, 17</sup> Acetyl-beta-methylcholine should be administered by mouth in doses of 1 to 1.5 gm. We do not know the ideal dosage of papaverine hydrochloride: we have injected as much as 4 grains (0.24 gm.) subcutaneously and as much as 0.5 grain (0.032 gm.) intravenously in cases in which patients did not have vascular diseases, and these doses did not produce untoward effects of any importance. As a routine procedure it appears advisable to administer 0.25 grain (0.016 gm.) of papaverine hydrochloride intravenously, and to double this amount in thirty minutes if evidence of vasodilatation does not occur and if untoward effects are not noted. Injections can be repeated as needed if the first or second

one causes an increase in circulation to the extremity. At present our opinions regarding the efficacy of papaverine are *sub judice*; further observations are needed. If a machine, such as the ones constructed and described by Reid and Herrmann, by Landis and Gibbon, and by Krusen, is available, it should be used promptly, either alone or in combination with the vasodilating drugs indicated. Spinal anesthesia may be administered if the arteries of the legs are occluded and if the condition of the patient warrants it. Emmett has shown that maximal vasodilatation in the lower extremities follows this procedure. Theoretically, anesthetization of the brachial plexus should induce increased blood flow to the upper extremities. The artificial induction of fever by the intravenous injection of typhoid vaccine causes peripheral vasodilatation, as has been shown by Brown and others,<sup>4</sup> although its use in instances of sudden arterial occlusion is open to question because of the unpleasant side effects. Some of these unpleasant effects may be avoided by the artificial induction of fever by the intramuscular injection of sulphur in oil, which likewise produces vasodilatation, although pain at the site of injection may be severe.<sup>20</sup> Sympathectomy ordinarily is not indicated because it is a major surgical procedure and because the same results can be obtained temporarily with some of the methods which have been described.

Much that has been said about treatment is theoretical, but logical and true evaluation will depend on repeated clinical observation. Opportunities for this are rare as one seldom has the opportunity to treat a patient shortly after a main artery has been occluded suddenly. It may be well to theorize as to why prompt treatment is advisable. It has been known for a long time that the number of cases in which embolectomy is successful is inversely proportional to the time elapsing between the onset of embolism and the surgical procedure. The reason for this is not entirely clear, and it is not entirely clear why treatment must be prompt to be valuable in arterial thrombosis which occurs suddenly. It is certain, however, that failure to relieve spasm or to induce arterial dilatation, after either of these conditions occurs, leads to profound ischemia of the limb in most cases. If ischemia persists for several hours, it appears that the intima of both arteries and veins is so badly damaged that, when vasodilatation is accomplished, widespread vascular thrombosis occurs and ischemia becomes permanent instead of transient, as it would if vasodilatation had been induced soon after sudden arterial occlusion had occurred.

#### CONCLUSIONS

1. Arterial thrombosis may occur suddenly as a primary clinical manifestation of thromboangiitis obliterans. This situation occurred in 11 of our series of 255 cases, or, roughly, in 4 per cent. None of the patients were under our observation at the time occlusion occurred. Amputation was eventually necessary in two cases (18 per cent).

2. Arterial thrombosis may occur suddenly in the course of well-developed thromboangiitis obliterans. This situation occurred in fifteen, or 6 per cent of our series of 255 cases. Only two of the patients were under our observation at the time occlusion occurred. Amputation of a leg was subsequently necessary in 10 cases (66 per cent).

3. Treatment, which should be begun promptly, consists of relief of pain, avoidance of burning the limb, and the relief of arterial spasm, or the induction of vasodilatation, by means of drugs, intermittent negative and positive pressure, artificially induced fever, or anesthesia.

#### REFERENCES

1. Allen, E. V., and MacLean, A. R.: Treatment of Sudden Arterial Occlusion With Papaverine Hydrochloride: Report of Case, Proc. Staff Meet. Mayo Clin. 10: 216, 1935.
2. Barker, N. W.: Thrombo-angiitis Obliterans With Occlusion of Both Femoral Veins and Both Popliteal Arteries, Med. Clin. North America 15: 233, 1931.
3. Brown, G. E.: Thrombo-angiitis Obliterans, Surg. Gynec. Obst. 58: 297, 1934.
4. Brown, G. E., Allen, E. V., and Mahorner, H. R.: Thrombo-angiitis Obliterans; Clinical, Physiologic and Pathologic Studies, Philadelphia, 1928, W. B. Saunders Company.
5. Buerger, Leo: The Circulatory Disturbances of the Extremities Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, 1924, W. B. Saunders Company.
6. Cook, E. N., and Brown, G. E.: The Vasodilating Effects of Ethyl Alcohol on the Peripheral Arteries, Proc. Staff Meet. Mayo Clin. 7: 449, 1932.
7. Denk, Wolfgang: Zur Behandlung der arteriellen Embolie, München. med. Wchnschr. 81: 437, 1934.
8. Emmett, J. L.: Subarachnoid Injections of Procaine Hydrochloride: the Quantitative Effects of Clinical Doses on Sensory, Sympathetic and Motor Nerves, J. A. M. A. 102: 425, 1934.
9. Goldsmith, Grace A.: The Vasodilating Effects of Acetyl B-Methylcholine, Proc. Staff Meet. Mayo Clin. 9: 337, 1934.
10. Herrmann, L. G., and Reid, M. R.: The Conservative Treatment of Arteriosclerotic Peripheral Vascular Diseases: Passive Vascular Exercise (Pavaex Therapy), Ann. Surg. 100: 750, 1934.
11. Horton, B. T., and Brown, G. E.: Thrombo-angiitis Obliterans Among Women, Arch. Int. Med. 50: 884, 1932.
12. Krusen, F. H.: Passive Vascular Exercise for Diseases of Peripheral Vessels; Description of a New Device, Arch. Physical Therapy 16: 581, 1935.
13. Landis, E. M., and Gibbon, J. M., Jr.: Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities, Proc. Soc. Exper. Biol. & Med. 30: 593, 1933.
14. McGovern, Teresa, McDevitt, Ellen, and Wright, I. S.: Theobromine Sodium Salicylate as a Vasodilator, J. Clin. Investigation 15: 11, 1936.
15. McKechnie, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities: A Study of 100 Cases of Embolism and Thrombosis, Proc. Staff Meet. Mayo Clin. 10: 678, 1935; Surg. Gynec. Obst. 63: 231, 1936.
16. Mulvihill, D. A., and Harvey, S. C.: Studies on Collateral Circulation: I. Thermic Changes After Arterial Ligation and Ganglionectomy, J. Clin. Investigation 10: 423, 1931.
17. Newell, C. E., and Allen, E. V.: The Peripheral Vasodilating Effect of Theobromine Given Orally and Intravenously, J. Tennessee State M. A. 27: 291, 1934.
18. Reid, M. R., and Herrmann, L. G.: Treatment of Obliterative Vascular Diseases by Means of Intermittent Negative Pressure Environment, J. Med. 14: 200, 1933.
19. Scupham, G. W.: Effect of Theobromine on Peripheral Vascular Disease; Clinical Observations, Arch. Int. Med. 54: 685, 1934.
20. Waller, L. M., and Allen, E. V.: The Use of Sulphur for the Production of Fever in Peripheral Vascular Diseases, Ann. Int. Med. 5: 478, 1931.

# Department of Clinical Reports

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## METASTATIC CARCINOMA OF THE HEART

### A CASE PRESENTING AURICULAR FLUTTER, SYMPTOMS OF CORONARY THROMBOSIS, AND CONGESTIVE HEART FAILURE\*

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**C**ARCINOMA of the heart is usually metastatic, and in most cases the symptoms due to the primary process, or other metastases, are so conspicuous in the clinical course of the patient that it proves difficult, even in retrospect, to ascertain the part played by the involvement of the heart. The case reported here is one of bronchogenic carcinoma in which symptoms and signs produced by the metastasis to the heart dominated the clinical course. The case provided an interesting diagnostic problem inasmuch as a hemorrhagic pericarditis due to malignancy of the pericardium appeared to be the cause of symptoms suggesting both an acute surgical condition of the abdomen and acute coronary thrombosis. It is also noteworthy for several other characteristics that are among the less common findings in metastatic carcinoma of the heart.

#### CASE REPORT

*History.*—The patient, P. S., was admitted to Sea View Hospital, April 4, 1934. He was a white male, German by birth, aged forty-nine years. He was a chauffeur. His family history was negative. His past history was also essentially negative. He did not drink or smoke. He had been in good health and had maintained his body weight.

The duration of the history from the beginning of any symptoms or signs of illness until death was approximately nine months, and this can be divided into four periods: (1) A period of five months in which the chief symptoms were those of peptic ulcer (from November, 1933, to April, 1934). (2) A period of 11 weeks in which there was vomiting of small quantities of blood from time to time (from March 4, 1934, to May 25, 1934). (3) A period of six days in which coughing with hemoptysis occurred (from May 25, 1934, to May 31, 1934). (4) The cardiac period (symptoms resembling coronary thrombosis, an attack of auricular flutter, congestive heart failure) lasting thirteen days (from Aug. 15, 1934, to Aug. 28, 1934).

In the first period of five months he suffered pain in the left hypochondrium, recurring in episodes and relieved by food. A series of x-ray films of the gastrointestinal tract before he entered the hospital had established a diagnosis of peptic ulcer. He was refused operation for the peptic ulcer because of abnormal pulmonary signs suggesting tuberculosis, for which he was admitted to Sea View Hospital.

*Physical Examination.*—The patient was a well-developed, well-nourished adult male, showing no signs of acute illness. His weight upon admission was 139 pounds;

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it increased to 158, and again declined to 151 pounds. A general physical examination yielded essentially negative results, except for the signs in the thorax and abdomen. The lungs showed bronchovesicular breathing, with fine râles over the right upper lobe. The heart was moderately enlarged. The heart rate was 80 a minute. The rhythm was normal. The sounds were of normal quality. There were no murmurs. The blood pressure was 130/90. The abdomen showed slight tenderness in the right lower quadrant and in the epigastrium.

The urine showed a faint trace of albumin with occasional white blood cells and epithelial cells. The blood Wassermann reaction was negative. The blood count showed the following: Red blood cells, 4,470,000; hemoglobin, 80 per cent; polymorphonuclears, 61 per cent; lymphocytes, 28 per cent; monocytes, 7 per cent;



Fig. 1.—Roentgenogram taken April 16, 1934. Note lesion in right apex with displacement of trachea and mediastinum to the right; also essentially normal cardiac shadow.

nonsegmented polymorphonuclears, 1 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent. The sedimentation rate of red blood cells was 47 mm. in forty-five minutes.

The x-ray examination of the gastrointestinal tract revealed an irregular filling of the cap and confirmed the diagnosis of peptic ulcer. The x-ray film of the thorax showed retraction and atelectasis of the right upper lobe with shifting of the trachea and mediastinum to the right (Fig. 1). This was interpreted as an end-stage of a caseous pneumonic tuberculous lesion. The results of repeated sputum examinations were negative for tubercle bacilli. The patient refused a bronchoscopic examination, and with the facts at hand the diagnosis of tuberculosis could not be established, nor the possibility of malignancy excluded.

*Course.*—His only complaints in the first seven weeks after his admission were those which were interpreted as due to the peptic ulcer, namely, pain in the epigastrium coming on an hour after meals and relieved by food, and from time to time vomiting of blood-tinged material. The patient received a Sippy diet and moderate improvement ensued. He then began to cough up small amounts of material with bright red blood intimately mixed with the sputum. This subsided after six days, following which he remained practically symptom-free for ten weeks (from May 31, 1934 to Aug. 15, 1934).

He was being considered for discharge from the hospital when the terminal episode started. There was a sudden severe attack of pain in the epigastrium with persistent vomiting for more than forty-eight hours. Two days following the onset, the patient looked extremely ill. The extremities were cold and clammy. The heart sounds were of poor quality and the rate very rapid. By the third day a friction rub was heard in the fourth intercostal space to the left of the sternum. An electrocardiogram showed a right axis deviation and auricular flutter with a 2:1 A-V block and a ventricular rate of 176 a minute. Marked rigidity was noted in the epigastrium and right upper abdominal quadrant. There was a rise of temperature to 100.4° F. The blood pressure throughout this period continued unchanged, namely, between 126/84 and 134/96. On the fourth day a sinus rhythm with a rate of 90 a minute had replaced the flutter. Diffuse signs appeared throughout both lungs—sibilant, sonorous, and fine moist râles. On the seventh day an area of localized swelling was seen on the right side of his neck due to a venous thrombosis. The electrocardiograms taken on the fifth and seventh days were similar and showed a sinus rhythm of 90 a minute, right axis deviation, and cove-plane T-waves in Leads I and II. There was no displacement of the R-T segments.

His condition became progressively worse. Heart failure with congestion developed; the liver became enlarged; edema appeared in the right side of the thorax and in the sacral region; and a right hydrothorax developed. The heart sounds grew barely audible. The temperature rose to 101° F. The white blood cell count rose to 17,850 with 83 per cent polymorphonuclears on Aug. 27, 1934. He died Aug. 28, 1934, thirteen days after the first appearance of symptoms referable to the heart.

The severe abdominal pain with vomiting, fever, and muscular rigidity, and the history of peptic ulcer, directed attention to a possible acute surgical condition of the abdomen. The signs of shock, the auricular flutter, the pericardial friction rub, suggested, on the other hand, a coronary thrombosis with symptoms referred to the right upper abdominal quadrant. This received some support from the electrocardiographic abnormalities seen when the normal sinus rhythm was reestablished. These and other diagnoses were entertained. The post-mortem examination failed to sustain them.

*Autopsy.*—The significant findings in the post-mortem examination were as follows:

1. A radial scar of a healed peptic ulcer was present in the duodenum just beyond the pylorus.
2. There was a right pleural effusion of 3,000 c.c. of pale yellow fluid.
3. A carcinoma involving the right main bronchus and the right upper lobe bronchus was found, with invasion of most of the right upper lobe. It invaded the right lower lobe posteriorly by lymphatic extension. The middle lobe was compressed but escaped metastasis.
4. There was no gross metastasis to the left lung, but in the microscopic examination small areas of tumor cells in the lymph spaces were found in the pleura of the left upper lobe. There was a thrombosis of a fairly large vessel in the midportion of the left upper lobe, with pulmonary infarction. The infarction may have been due to a primary pulmonary thrombosis or to an embolus from the venous thrombosis in the neck.

5. In the microscopic examination, the superior and inferior tracheobronchial nodes proved to be involved extensively.

6. There was a very dark, almost black, bloody, pericardial effusion of 300 c.c. Both layers of the pericardium were greatly thickened, especially the parietal, and their endothelial surfaces over all the chambers were studded with numerous indurated yellowish nodules about 1 to 2 mm. in diameter, covered by smooth, shining membrane (Fig. 2). The heart with the pericardium weighed 585 gm. and without the parietal pericardium, 250 gm. The appearance of the endocardium was normal. The aorta showed a few atheromatous plaques. Similar plaques were also present at the mouths of both coronary vessels but did not, however, reduce the size of



Fig. 2.—Post-mortem appearance of heart and pericardium. Note relative thickness of myocardium and pericardium.

the lumen appreciably. A careful search of the coronary vessels disclosed moderately advanced sclerosis of the arteries, but failed to reveal any thrombosis or areas of myocardial infarction.

7. The remainder of the complete pathological examination was substantially negative, except for those changes seen in congestive heart failure. The liver and spleen were moderately enlarged, the former weighing 1,890 gm., and the latter 125 gm.

The malignant tissue was squamous cell carcinoma. Fifty slides of tissue from the heart and the pericardium were examined, and in 11 several areas of sections from representative portions were inspected microscopically by each of three observers, who made independent estimates of the amount of malignant tissue in a

given area. The agreement between these estimates was usually very close and the averages were recorded. Malignant tissue was found to represent approximately 5 to 85 per cent of the cells seen in sections of the pericardium from various portions of the auricles and ventricles. In very few of the slides were malignant cells found in the myocardium. These areas were small, involving only about 5 per cent of the areas of the muscle examined, and, with only one exception, adjacent to the pericardium. In one slide of the interauricular septum about 60 per cent of the field represented malignant tissue.

#### COMMENT

The noteworthy characteristics of this case may be considered briefly as follows:

1. There was extensive invasion of the parietal and visceral pericardium, the myocardium remaining almost free from malignant tissue. The escape of the myocardium in cases in which both layers of the pericardium are extensively involved is an unusual finding. One such case was published by Campagna and Hauser.<sup>1</sup>

2. Since the tumor tissue in the pericardium was confined to the lymphatic spaces, there can be little doubt that the metastasis occurred through the lymph vessels. Except for those cases in which the heart is invaded by direct extension from massive thoracic malignancies, metastasis to the heart, in the majority of cases, is believed to take place through the blood stream.<sup>2, 3</sup>

3. The hemorrhagic pericardial effusion found at autopsy in this case is also an unusual finding in metastatic carcinoma of the heart. Usually metastatic carcinoma of the pericardium fails to produce an effusion of any kind.<sup>1</sup> However, when a hemorrhagic pericardial effusion is discovered during life, it provides fairly strong evidence of pericardial malignancy.<sup>4</sup>

4. Auricular flutter is also rare among the cases of carcinoma of the heart. Fishberg<sup>5</sup> recently reported three cases of auricular fibrillation and flutter in which tumor tissue infiltrated the auricular wall through to the endocardium. In our case the tumor tissue in the auricular muscle was confined to small groups of cells in the interauricular septum. The mechanism by which malignant tissue gives rise to auricular fibrillation or flutter is obscure. It seems likely that if a mechanical factor is responsible, it operates through interference with the circulation to the auricular musculature, since the abnormal rhythm may be paroxysmal (as in our case and in two of the three cases reported by Fishberg).

5. Thoracic pain is fairly common in patients with cardiac malignancy. It is usually impossible, however, to ascertain whether the pain is due to the involvement of the heart or of other mediastinal tissues. One of Fishberg's patients<sup>5</sup> suffered an attack of substernal pain attended by other symptoms which suggested coronary thrombosis. At autopsy, tumor tissue was found completely surrounding the circumflex branch of the left coronary artery, narrowing its lumen, and this was suggested as the possible cause of the attack of pain. In our patient,

the hemorrhagic pericarditis appears to be the most likely explanation of the sudden attack of pain with signs of circulatory collapse and auricular flutter, which had the clinical appearance of a coronary thrombosis or, because of the location of the pain, an acute surgical condition of the abdomen. The only other possible explanation found at autopsy is the infarct in the upper lobe of the left lung. This undoubtedly contributed to the fatal outcome but seems less likely as the primary cause of an attack of pain with muscular rigidity in the right upper abdominal quadrant.

An early reviewer of the subject of cardiac malignant disease<sup>4</sup> called attention to the surprisingly good functional capacity of the heart which is the seat of extensive invasion by malignant tissue. In our case, extensive involvement of the visceral and parietal pericardium covering all the chambers prevailed, without any appreciable cardiac insufficiency. Hamilton<sup>6</sup> reported a case in which the myocardium was almost completely replaced by malignant tissue, with relatively mild disturbance of the circulation. These serve to illustrate the large margin of safety in the heart muscle against gradually applied mechanical obstacles, provided the muscle remains free of toxic influence. It presents a marked contrast to the rapidly failing heart in toxic states in which serious impairment of the functional capacity of the heart occurs, when relatively little gross structural change is in evidence.

The course of cancer of the heart is likely to be fairly rapidly fatal, however, after the beginning of symptoms referable to the heart. In our case, death occurred with congestive heart failure within thirteen days after the onset of cardiac symptoms.

#### REFERENCES

1. Campagna, M., and Hauser, G. H.: A Malignant Condition of the Pericardium, *J. A. M. A.* 90: 1362, 1928.
2. Mead, C. H.: Metastatic Carcinoma of the Heart Secondary to Primary Carcinoma of the Lungs, *J. Thoracic Surg.* 2: 87, 1932.
3. Morris, L. M.: Metastases to the Heart From Malignant Tumors, *AM. HEART J.* 3: 219, 1927.
4. Link, R.: Die Klinik der primären Neubildungen des Herzens, *Ztschr. f. klin. Med.* 67: 272, 1909.
5. Fishberg, A. M.: Auricular Fibrillation and Flutter in Metastatic Growths of the Right Auricle, *Am. J. M. Sc.* 180: 629, 1930.
6. Hamilton, R. L.: Metastatic Carcinoma of the Heart, *Am. J. Cancer* 16: 205, 1932.

## CARDIAC METASTASIS FROM CARCINOMA OF THYROID\*

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CARCINOMA of the thyroid gland is not a rarity and is often diagnosed clinically before metastases occur. Occasionally distant metastases, especially in bone, focus attention on the thyroid as the primary source. Of such metastases, described in many organs, the rarest seem to be those to the heart. A careful review of the literature revealed but twelve cases. To these we add one which recently came under our observation.

### REPORT OF CASE

On July 18, 1935, K. O., female, aged sixty-nine years was admitted to the Home for Incurables complaining of pain in the right hip and inability to move her right leg.

Family history was negative. Twenty-eight years before patient had had panhysterectomy for metrorrhagia and menorrhagia; three years before she had had an attack of cardiac decompensation.

One year before admission, onset of pain in the right hip, concomitant weakness, loss of weight, and belching after eating. One month later swelling and pain in the left ankle developed. Ten days before admission she felt her right leg snap at the hip without associated trauma and was unable to move her leg. No complaints referable to the thyroid; no swelling or lump was ever noticed by her.

Physical examination revealed a thyroid moderately enlarged to the right, somewhat firm; bronchial breathing in the right lower interscapular region with râles at both bases; right leg shortened, mobility preternatural at the right hip which was thicker than the left hip; swelling of the left ankle.

X-ray films showed fracture of right femoral neck with absorption of the outer half of the neck and all of the greater trochanter. Just above the left ankle joint the bones of both tibia and fibula were absorbed almost completely for almost one-fifth of the calf length. Bence-Jones protein was found in the urine. Blood count was 3,800,000, R.B.C.; hemoglobin, 60 per cent; 9,400, W.B.C.; lymphocytes, 35 per cent; eosinophiles, 3 per cent.

She became rapidly and progressively weaker, lost weight, and died two months after admission.

The clinical impression was metastatic malignancy, primary focus uncertain. Both gastrointestinal tract and thyroid were considered as primary foci.

*Autopsy.*—The thyroid was completely replaced by a firm mass in the right side of the neck and in midline, not compressing the trachea and easily separated from it. It measured 6 by 4 by 2 cm. and was covered by a capsule which was

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adherent to the surrounding fascia. On section a lobulated pinkish yellow homogeneous tissue bulged over the cut edge. There were small remnants of compressed beefy granular tissue containing calcific material at both upper and lower poles. Toward the right of the thyroid was found a large gland, 3 by 2 by 2 cm., its parenchyma completely replaced by tissue similar to that in the thyroid. Thyroid veins, jugular, subclavian, and innominate veins and superior vena cava were not grossly involved by tumor or thrombi.

The right pleural cavity contained 250 c.c. of a thin brown fluid and veil-like adhesions attached the lung to the anterior parietes and diaphragm. Both lungs presented a diminution of crepitation, edema, and a diffuse infiltration with small pink homogeneous nodules. The latter were prominent in the lower lobes and projected to the pleura. The right lower lobe was atelectatic and contained a great number of nodules.

The pericardial sac contained little serous fluid. The musculature was pale and flabby, and both ventricles were somewhat dilated. The right ventricular walls measured 0.4 cm. in thickness, and embedded in the right lateral wall, 3 cm. above the apex, was a spherical nodule. The nodule was of homogeneous pink color, measured 1 cm. in diameter, and reached to, but did not perforate, the endocardium. Thin musculature and epicardial fat bounded the nodule laterally. No other gross pathology was present.

There was no increase in peritoneal fluid. The liver presented accentuation of the central veins. On the upper right surface two small pink nodules projected through the peritoneal lining, one of which was umbilicated. Both nodules were soft and were surrounded by a narrow hemorrhagic zone.

In the lower pole of the right kidney a nodular mass occupied the parenchyma from the pelvis to, and causing bulging of, the capsule. The structure was similar to the other nodules except that radial striations were noted. Otherwise both kidneys were pale and unaltered. Uterus and adnexa were absent. The remaining abdominal organs merely showed cloudy swelling.

The head of the femur was freely movable from the neck and partially surrounded by a soft, slight, gritty pinkish white mass which replaced the neck, trochanter, and part of the upper shaft. Both marrow cavity and bone were replaced by this soft tissue mass 6 cm. thick and lined externally by a thickened continuation of the periosteum. The mass extended 8 cm. below the head of the femur, and the marrow cavity was red for 9 cm. below this level. The center of the growth was necrotic. The cortex immediately below the mass was sclerotic and widened to 0.6 cm. The left ankle presented a complete replacement by a similar growth in the lower fifth of the tibia and fibula.

*Microscopic Examination.*—The thyroid mass consisted of lobules separated by thick hyaline connective tissue. The lobules contained sheets of cells without arrangement, columns of cells with occasional irregular gland formation, and many groups of acini containing acidophilic cytoplasm and moderately hyperchromatic large oval nuclei. Occasional mitotic figures were demonstrable. Vascularity was pronounced and venules occasionally presented a partial lining by thyroid cells. An occasional plug of thyroid cells was found within the lumina of veins. No capsule was demonstrable, the glandular tissue invading the fibrous tissue in the neighborhood.

The lymph gland to the right of the thyroid was completely replaced by similar thyroid tissue, but the capsule was not invaded and the interlobular septums were thin. All the nodules grossly visible consisted of thyroid acini in more or less irregular formation containing colloid.

In the lower and middle lobe of the right lung, thyroid tissue occupied as much space as the lung parenchyma. The alveoli were atelectatic, forming by their parallel compressed arrangement poorly developed pseudocapsules for the thyroid growths, no fibrous tissue reaction occurring. The right upper lung contained several scattered nodules, the alveoli were emphysematous and contained albuminoid transudate.



Fig. 1.—Photomicrograph of thyroid nodule in the myocardium. The atrophic heart muscle appears at the upper right.

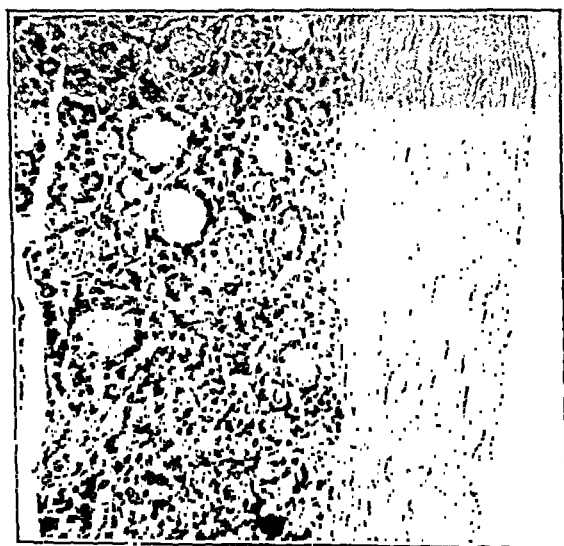


Fig. 2.—Photomicrograph of thyroid nodule in the subendocardial tissue. Note the thickened endocardium in the right midfield covering the metastatic tissue.

The left lung presented a similar picture, though not so pronounced. In both lungs the tiny nodules were demonstrable within the alveoli attached to alveolar septums in direct relation to the capillaries. Both lungs were intensely congested.

The heart muscle presented a slight patchy fibrosis and slight intimal thickening of the smaller coronary arteries. The nodule consisted of thyroid tissue with no lobular arrangement other than suggested by strands of hyalinized muscle fibers



caught in the growth. Acini infiltrated the surrounding muscle fibers, which were thinned and degenerated. The endocardium, though bulging, was thickened and not infiltrated.

The liver nodules consisted of thyroid acini, mostly small, without colloid. The surrounding liver cords were degenerated, compressed, and infiltrated by the glands. No fibrous tissue reaction had occurred. Otherwise the liver cells were hazy and granular.

The kidney parenchyma was compressed and infiltrated by the nodule of thyroid acini and cords of cells. Moderate fibrosis and round cell infiltration occupied the surrounding degenerating kidney substance. An occasional interlobar artery contained tumor emboli. The tubular epithelium was hazy and granular. An occasional interlobular artery presented intimal thickening, with narrowing of lumen and shrinking, even fibrosis, of the glomeruli. The spleen presented a hyperplastic splenitis. The adrenals and pancreas were unaltered.

The neck of the femur was occupied by thyroid tissue similar to that in the primary growth. Bits of bone were scattered in the mass, and larger necrotic areas were present deeper in the growth. The periosteal lining of the mass was thick, fibrous, and dense. The cortex adjacent to the growth consisted of dense, thick trabeculae of bone with relatively few cells. The medulla below the growth consisted of hyperplastic hematopoietic marrow, especially pronounced around neoplastic nodules. The left ankle presented a similar microscopic picture.

*Diagnosis.*—1. Adenocarcinoma of the thyroid infiltrating the surrounding tissue, metastasizing both by lymph and blood stream. 2. Right-sided serofibrinous pleurisy. 3. Right lower lobe atelectasis. 4. Cloudy swelling of parenchymatous organs.

The clinically relatively slight enlargement of the thyroid, and the absence of other evidence pointing toward the thyroid, were features. This, together with the gastrointestinal complaints and the presence of Benec-Jones protein, prevented the clinicians from arriving at a definite diagnosis.

Pathologically the main features were the relatively small primary growth, associated with numerous vascular metastases, the intense seeding of both lungs, the unusual myocardial metastasis, and the large growths in the lower extremities.

#### COMMENT

The study of metastases of carcinomas of the thyroid has occupied the attention of many authors in extensive reviews (Wegelin,<sup>1</sup> Barthel,<sup>2</sup> Ehrhardt,<sup>3</sup> Smith<sup>4</sup>). The conclusion generally reached is that invasion of the heart constitutes a rare finding, most reviewers having come across single cases in the literature.

Likewise carcinoma metastatic to the heart has been intensively reviewed (Goldstein,<sup>5</sup> Yater,<sup>6</sup> Morris,<sup>7</sup> Burke,<sup>8</sup> Ewing,<sup>9</sup> White<sup>10</sup>). In these reviews, though stating the possibility of primary source in any of the parenchymatous organs, the thyroid is not included in the enumeration. Metastatic carcinoma to the heart is so infrequent as to occasion interest and comment on its discovery. Nicholls<sup>11</sup> in 1927 reviewed 36,980 cases of carcinoma proved by autopsy. He found cardiac metastases in 109 cases, i.e., in 0.28 per cent of carcinoma.<sup>11</sup>

Nevertheless, a thorough search in the literature reveals a number of cases of cardiac invasion secondary to primary carcinoma of the thyroid, most of which are not listed by the reviewers.

Carcinomatous involvement of the heart from a primary neoplasm in the thyroid gland is of two types. In the first type, the right cardiac chambers are filled, to greater or lesser extent, by tumor thrombus reaching them by direct extension from the thyroid veins by way of the superior vena cava. This type more properly should be called neoplastic thrombosis rather than cardiac metastasis. In such instances the symptoms and signs are those of venous obstruction particularly in the head and neck, sudden dyspnea, and general venous stasis in the peripheral circulation. Death ensues in a manner similar to that in cases of massive pulmonary embolism. Of this type the following cases are recorded.

Kaufmann<sup>12</sup> described the case of a fifty-eight-year-old female with a goiter of twenty-eight years' duration. She suddenly developed difficulty in breathing and swallowing and edema and cyanosis of her face, upper extremities and chest; she died six months after the onset of the initial symptoms with the picture of acute obstruction of the pulmonary circulation. Autopsy disclosed a massive carcinomatous replacement of the thyroid. The neoplasm extended into the thyroid veins. Tumor thrombus filled the jugular and subclavian veins and the superior vena cava. The right auricle was completely filled with tumor thrombus; there was no invasion of the myocardium or endocardium. The cervical and mediastinal lymph nodes contained tumor; metastases were present in the lungs.

Holt's case<sup>13</sup> was that of a seventy-two-year-old male with known thyroid tumor of one year's duration. The thyroid mass had receded for two years following radiation therapy, but for a year there had been respiratory distress, slowly increasing cyanosis of the head, neck, and right arm, and edema of the legs. Attacks set in and rapidly increased in frequency and severity during the last three months, concomitantly the cyanosis becoming more intense. Death ensued in such an attack. Heart sounds, rate, and blood pressure were always normal. At autopsy the thyroid was found replaced by a firm tumor that extended into both innominate veins, filled the superior vena cava and right subclavian and internal jugular veins, and entered the right auricle. This cavity was filled with a polypoid tumor thrombus which was adherent to but did not infiltrate into the endocardium. There were no other metastases. Sections of thyroid and thrombotic mass were composed of adenocarcinoma.

Wylegschanin<sup>14</sup> reported the case of a fifty-two-year-old female who suddenly developed difficulty in breathing; a cough; a feeling of pres-

sure over the heart; edema of face, arms and abdomen; and cyanosis. There was a known thyroid enlargement of many years' duration. The heart sounds were muffled; the heart was not enlarged clinically. Death ensued one year from onset of respiratory distress and formation of mass in the neck. At autopsy, the lungs were markedly collapsed and congested, the lower lobes completely atelectatic; there was a large bilateral bloody pleural effusion. The pericardial sac contained 150 c.c. of clear fluid. The heart was enlarged by a marked dilatation of the right auricle and, to a lesser extent, of the right ventricle. This auricle was completely filled by a large tumor mass adherent to the posterior wall at the sino-auricular junction, but extending thence backward into and almost filling the superior vena cava, internal jugular and innominate and subclavian veins to the thyroid; even the vena azygos contained a thrombus. In the right ventricle a few small thrombi were loosely adherent to the endocardium between the trabeculae and behind the posterior tricuspid leaflet. The thyroid was converted into a dense, firm, gray white mass, sections of which, as well as sections of the thrombi, were composed of compact masses of irregularly cubical epithelium in places forming irregular and incomplete acini containing a little colloid. There were local lymph gland metastases and invasion into the sternothyroid and sternohyoid muscles; there was no extension into the endocardium and no pulmonary or distant visceral metastases.

Mencarelli<sup>15</sup> reported the case of a fifty-seven-year-old male who suddenly developed cyanosis and edema of the face and upper extremities. There were no cardiac symptoms or symptoms referable to the thyroid gland. Death ensued shortly after admission to the hospital, with the picture of acute edema of the lungs; total duration of symptoms from the onset was less than two months. At autopsy a large tumor was found replacing the thyroid gland and extending for some distance up and down the neck beyond the gland capsule. The right internal jugular vein was completely filled by a soft red yellow tumor thrombus. The innominate veins and superior vena cava were not grossly involved. The right auricle was dilated and hypertrophied. The right ventricle was filled by a tumor mass 6 by 4.5 cm., adherent to the anterior and posterior walls but not extending into them. There was only a small residue of ventricular lumen remaining on the anteromedial aspect between the interventricular wall and thrombus. The thrombus raised the tricuspid valve cusps so that they were in the position of closure and in contact. There were multiple tumor nodules in the lungs and one in the right kidney. All the viscera showed acute passive congestion. Histologically the thyroid tumor, venous and cardiac thrombi, and pulmonary and renal metastases were composed of masses of anaplastic and giant epithelial cells; a tendency to acinar arrangement was

present, but there was no colloid. No arteries, even to precapillary size, were invaded. The thyroidal venules were extensively invaded and filled with tumor thrombi.

The second type of cardiac involvement is truly metastatic in character. In this type the thyroidal veins may be invaded, but this is a microscopic finding. There is no dilatation of the cervical veins or the vena cava and no tumor or other thrombosis; nor do the cardiac chambers contain tumor thrombi. Metastatic foci are widespread throughout the body, involving especially the lungs and kidneys. In the heart the metastases are frequently deep within the ventricular musculature or, less frequently, the auricular musculature, but they may reach the endocardium. There is no recorded case of perforation through the endocardium, although there may be a reactive thrombo-endocarditis. In two instances foci were present in the interventricular septum.<sup>19, 20</sup> There is a longer interval between the initial symptoms and death. Attention is usually focused either on the thyroid tumor or, more often, on the bony metastases. Cardiac symptoms are lacking in the recorded cases; there is no record of electrocardiographic studies. Such dyspnea as is present is not associated with cyanosis or edema and seems to be due entirely to local pressure on the trachea or larynx. Of this type, of which our case is an example, the following cases are recorded:

Berard and Dumet's case<sup>16</sup> occurred in a fifty-eight-year-old male. No clinical history is appended. In the heart muscle were two nodules near the apex, the one in the right ventricle dipping deeply and extending to the endocardium, which was covered locally by a noncarcinomatous vegetation. In the left ventricular myocardium was a small sub-endocardial node. Metastases were present in the lungs, kidneys, and regional lymph nodes.

Van Straaten<sup>17</sup> reported a case in a fifty-five-year-old male with a seven-month history of enlargement of the neck, associated with pain locally and with ulceration (of the skin?). At autopsy metastases were recorded in the heart muscle, lungs, liver, and kidneys without further details. He further tabulated a series of thirty-five cases of carcinoma of the thyroid from Kundrat's Institute in Vienna, in which one case of myocardial metastasis occurred. No further details are given.

Ehrhardt<sup>3</sup> tabulated a series of 131 cases of carcinoma of the thyroid from Berne. Myocardial metastasis occurred once and pericardial metastasis once. No further details were recorded.

Thomsen<sup>18</sup> reported the case of a forty-year-old man with thyroid enlargement of four years' duration. Partial thyroidectomy was performed, the man living four and one-half years thereafter. Death was occasioned by the severe cachexia that developed. At autopsy there was found an adenocarcinoma involving the entire thyroid. There was pres-

sure on and invasion of the tracheal wall. The thyroïdal veins were filled (microscopically) with tumor thrombi. In the left ulna, at the site of a previous injury, was a metastatic tumor growth the size of a child's head. Five pea-sized metastatic tumor nodules composed of thyroid carcinomatous alveoli surrounded by a fibrous capsular-like structure were found in the heart. Two were situated endocardially in the left ventricular apex between the trabeculae, one in a similar location in the right ventricle, and one deep in the left ventricular apical myocardium, also one in the right auricular endocardium. Numerous metastases were present in the skin; each was ulcerated.

Eisen's case<sup>19</sup> occurred in a fifty-two-year-old woman with dysphagia and a sense of a lump in the neck for two years. During the next year pains developed all over the body; a mass was found in the right breast, right hip, and right frontal region. A cord and mass slowly and progressively grew in the left cervical region and right axilla. The left eyeball progressively became more protuberant; a left primary optic atrophy developed. Death ensued two years after the onset of symptoms. At autopsy the thyroid was found replaced by an adenocarcinomatous tumor. Metastases were present in the lungs, liver, pancreas, kidneys, long bones and spinal column, right adrenal gland, left orbit, and the dura of the middle fossa. In the heart were several small polypoid nodular excrecences on the endocardium and between the pectinate muscles; these, composed of tissue similar to that of the thyroid tumor, involved the endocardium but did not invade the myocardium. One nodule, of unrecorded size, was found in the interventricular septum 2 cm. below the aortic leaflet. It lay between endocardium and myocardium and did not invade either structure.

Kopelowitsch<sup>20</sup> recorded the case of a fifty-two-year-old female with a known goiter of nine years' duration. Menopause occurred at fifty years, and about one and a half years thereafter there occurred a sudden, rapid diffuse growth of the goiter resulting in pressure on the trachea and esophagus. The heart was somewhat enlarged, the sounds were muffled, and a systolic murmur was present over the entire precordium, especially over sternum and aorta. Blood pressure and pulse rate were not altered. Biopsy disclosed a carcinoma of the thyroid. Death ensued two months after the onset of symptoms. Autopsy revealed a large adenocarcinoma of the thyroid with metastases to the cervical and bronchial lymph nodes, the lungs, and left kidney. In the heart there was a large tumor nodule in the right ventricular myocardium, extending from the coronary sulcus to the ventricular apex and bulging into the ventricle but not perforating the thickened endocardium. Two small nodules were present deep in the right posterior ventricular myocardium, and one in the midinterventricular septum. The pericardial sac contained a turbid red exudate; the epicardium was covered with fibrin showing no tumor histologically.

Wirth<sup>21</sup> reported the case of a forty-eight-year-old female who lived for one year following a thyroidectomy for a rapidly growing cervical mass causing choking, dyspnea, and dysphagia. At autopsy there was found an anaplastic carcinoma of the thyroid, infiltrating esophagus and trachea to the bifurcation. Metastases were present in the lungs and kidneys. In the right ventricular myocardium there was a nodule of acinar and anaplastic thyroid tissue, gray yellow and soft, wedge-shaped, extending through the entire thickness in its midportion but not penetrating endocardium or pericardium.

Cardiac metastases per se have not, in the past, exhibited any special symptoms. They may be suspected if attention is paid to the occasional pericardial hemorrhagic effusion. It may be that detailed fluoroscopic studies indicating disturbances of contraction locally, or electrocardiographic studies pointing to conduction disturbances, may point the way to such a diagnosis in instances of thyroidal neoplasm. In striking contrast to the usual type of metastases from thyroid carcinoma is the relative freedom of bony involvement in cases in which metastases occurred in the heart. Still more striking is the rarity of remote metastases in cases of thrombotic extension of a thyroid carcinoma by way of the great veins to the cardiac chambers. This suggests that death ensued, by vascular occlusion, before the secondary pulmonic foci had broken into their veins and gained access to the general circulation. A suggestive corollary is the frequency of pulmonic metastatic nodules in those cases showing true myocardial or endocardial metastases and remote organ involvement.

#### SUMMARY

A case of primary carcinoma of the thyroid with myocardial metastasis is reported.

Twelve cases of cardiac involvement from thyroidal carcinoma, reported in the literature, are reviewed. The clinical and pathological distinction between thrombotic extension into the cardiac chambers and true metastases to the myocardium and endocardium is stressed.

Attention is called to hemorrhagic pericardial effusion as a suggestive diagnostic point in cases of cardiac metastasis. Detailed fluoroscopy and electrocardiographic studies are urged as an aid in such diagnosis.

The authors desire to express their thanks to Dr. Henry Joachim, chief of service of the Jewish Sanatorium for Incurables, and to Dr. Thomas A. Gonzales, acting chief medical examiner of the City of New York, for permission to report this case.

#### REFERENCES

1. Wegelin, E.: *Handb. d. spez. path. Anat. u. Histol.* Vol. 8, Berlin, 1926, Henke & Lubarsch.
2. Barthel, C.: *Ergebn. d. Chir. u. Orthop.* 24: 162, 1931.
3. Ehrhardt, O.: *Bruns' Beitr. z. klin. Chir.* 35: 343, 1902.
4. Smith, Pool, and Olcott: *Am. J. Cancer* 20: 1, 1934.
5. Goldstein, H. J., *New York M. J.* 115: 97, 1922.

6. Yater, W. M.: Arch. Int. Med. 48: 627, 1931.
7. Morris, L.: AM. HEART J. 3: 219, 1927.
8. Burke, E. M.: Am. J. Cancer 20: 33, 1934.
9. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, 1928, W. B. Saunders Co., p. 955.
10. White, P. D.: Diseases of the Heart, New York, 1931, The Macmillan Company, p. 434.
11. Nichols, P.: Canad. M. A. J. 17: 798, 1927.
12. Kaufmann, C.: Deutsche Ztschr. f. Chir. 11: 401, 1879.
13. Holt, W. S., Jr.: J. A. M. A. 102: 1921, 1934.
14. Wylegshanin, N. J.: Frankfurt. Ztschr. f. Path. 40: 51, 1930.
15. Mencarelli, L.: Cuore e Circulaz. 18: 532, 1934.
16. Mathieu, M. A.: (1881) quoted by Berard and Dumet in Cancer Thyroidien, Paris, 1924, Gaston Doin & Cie.
17. Van Straaten: Inaug. Dissertation, Freiburg, 1898.
18. Thomsen, C.: Burns' Beitr. z. klin. Chir. 115: 113, 1919.
19. Eisen, O.: Am. J. M. Sc. 170: 61, 1925.
20. Kopelowitsch, M. A.: Virchows Arch. f. Path. Anat. 288: 652, 1933.
21. Wirth, J. E.: Surg. Clin. North America 13: 415, 1933.

# THROMBOSIS OF A CORONARY VENOUS SINUS IN A CASE OF THROMBOPHLEBITIS MIGRANS\*

## CASE REPORT

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NUMEROUS cases of wandering and recurrent thrombophlebitis, particularly of the superficial veins, have been reported, and several of them have been suspected, but not proved, to have had involvement of a coronary vein during the course of their illness. In the case described in this report, the clinical picture a short time before death led to a diagnosis of thrombosis of a coronary vein. At post-mortem examination the coronary sinus opening into the right auricle was found to contain a yellow fibrinous mass completely occluding its lumen. None of the other cardiac vessels were thrombosed.

Earlier writers<sup>1, 2</sup> on the subject of migrating or wandering phlebitis appear not to have observed any complications arising from thrombosis of visceral veins, and considered the disease as affecting the peripheral veins only. More recently, however, it has been shown by a number of observers that similar conditions of thrombophlebitis may occur in various organs of the body, and thus give rise to symptoms much more alarming than are associated with thrombosis of peripheral vessels.

Since the papers of Moorhead and Abrahamson,<sup>3</sup> who first called attention to the presence of visceral venous thromboses, and Ryle,<sup>4</sup> who considered four additional patients who had had similar accidents, a number of reports have appeared describing venous thromboses in various organs, including lungs, brain, intestines, and heart. The evidence of cardiac involvement has been based upon symptomatology and physical findings only. Thus, Legrand<sup>5</sup> reports a case in a woman who, during the course of her disease, had attacks of tachycardia. Moorhead and Abrahamson believed that severe anginal pain accompanied by a rapid, fibrillating pulse indicated thrombosis of a cardiac vein. Coombs<sup>6</sup> mentioned several cases in which phlebitis preceded the onset of what appeared to be a mild cardiac infarction and suggested that some such attacks may be "due to a venous thrombosis less disastrous in its mechanical effect on the circulation through the walls of the heart" than an arterial obstruction would be. Hartfall and Armitage<sup>7</sup> have described a case in which there occurred severe precordial pain accompanied by breathlessness and palpitation of such severity that morphia had to be used. They considered this to be a coronary thrombosis al-

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though the electrocardiogram was normal. Campbell and Morgan<sup>8</sup> have described a doubtful case in which there were definite electrocardiographic changes. In none of these did the disease end fatally, and the diagnosis of cardiac involvement could not be confirmed. Our case is of particular interest in this respect since post-mortem examination confirmed the clinical diagnosis of thrombosis of a coronary vein.

#### CASE REPORT

Mr. B. H., aged forty-five years, was admitted to the Medical Service, Toronto General Hospital, November 19, 1932, and died May 14, 1933.

The patient was first seen on Sept. 20, 1932, complaining of a tender red streak along the lower right forearm, which had appeared on Sept. 10, 1932. Subsequently, a similar condition developed on the left leg. Previous history of note was that for twenty years he had had chronic postnasal discharge for which several intranasal operations had been performed. In August, 1932, he had an infected tooth extracted, and, ten days before the onset of the phlebitis in his limbs, there was discharge from an apical abscess above another tooth. The examination at the time of his first consultation showed typical superficial phlebitis of right arm and leg. Rest in bed was advised. The superficial phlebitis continued and on November 12 he suddenly became short of breath, perspired, felt chilly, and began to cough, bringing up a small amount of bloody sputum. He was advised to come into the hospital.

On admission to hospital, he was quite ill: temperature 104° F., and pulse rate 100; he had some respiratory distress. Chest examination showed diminished resonance and some râles at the right base. Patient improved, the temperature fell to normal, and the signs in his chest had practically disappeared by December 6. Repeated white blood counts were between 9,000 and 10,000. During this acute illness the phlebitis of the superficial veins of both arms and legs continued. It was of a migratory type, jumping from one limb to another.

On Jan. 6, 1933, he again had severe paroxysms of coughing with frothy, clear sputum and pleural pain on his right side; the temperature rose to 101° F. A pleural effusion developed rapidly and on January 11 blood-tinged fluid was aspirated from the right pleural cavity. At this time the phlebitis, which had continued since November to involve the superficial veins of all four limbs in a fitting manner, affected the deep veins of the left leg, which became markedly swollen and painful. No definite foci of infection were found in teeth, upper respiratory passages, etc. On January 28, he again had pleural pain on the left side of his chest; a friction rub was heard; and his cough and shortness of breath, which were not constant, became worse. There was some evidence of consolidation, and the change in his left chest was considered to be due to pulmonary infarction.

Migrating phlebitis of the veins of the limbs continued, a new area becoming involved every few days. In addition, almost constant dyspnea developed, which was markedly aggravated by severe paroxysms of coughing producing a slight amount of whitish sputum. He became weaker, and his dyspnea and cough were much more troublesome. On March 1, 1,000 c.c. of blood-tinged fluid was removed from his left chest. It was considered that the respiratory symptoms were due chiefly to repeated thromboses of the pulmonary veins with resulting infarction.

Since September, when the patient came under observation, occasional extrasystoles were present, but on March 6 he became very short of breath and complained that his heart felt as if it was beating very rapidly. Paroxysmal tachy-

cardia was found, with a rate of 160. These attacks of tachycardia persisted at intervals until his death on May 14. At no time was there complaint of pain in the chest, which was thought to be cardiac in origin. There was no evidence of ascites, dependent edema, or enlargement of the liver. An electrocardiogram taken first on March 6, when he had his initial attack of paroxysmal tachycardia, showed rate of 170, with voltage 5 mm., with  $T_{1,2}$  positive. On March 9 the tachycardia had disappeared, with  $T_{1,2}$  definitely negative; one month later voltage still 5 mm. with  $T_{1,2}$  biphasic. The changes in  $T_{1,2}$  were not typical of coronary thrombosis and, probably, were digitalis effects, as he was given this drug after his first attack of tachycardia. The repeated attacks of paroxysmal tachycardia, the constant and increasing dyspnea, along with evidence of thrombophlebitis involving the superficial and deep veins of the arms and legs and the pulmonary vessels, led to a provisional diagnosis of coronary venous thrombosis. There was nothing absolutely diagnostic of this, but the signs and symptoms of coronary venous thrombosis may have been masked by the extensive process in the pulmonary vessels.

Dyspnea and paroxysms of coughing became more marked, and the course was progressively worse. On May 14 he became markedly short of breath and died.

The temperature records from September, 1932, to May, 1933, usually showed some degree of fever—up to 100° F. The fever rose to 101° and 102° F. temporarily after pulmonary thrombosis, with occasional rises with widespread peripheral thrombosis. It was impossible to state whether the coronary venous thrombosis produced fever.

Repeated white blood counts ranged about 9,000, reaching a maximum of 12,000 on two occasions, with a differential count of about 70 per cent polymorphonuclears. Blood chlorides, 470 mg. per cent; carbon dioxide combining power, 57 volumes per cent; calcium, 9.5 mg. per cent; phosphorus, 4.5 mg. per cent; bleeding time, 3 minutes; coagulation time, 3 minutes 45 seconds; platelet count, 184,000.

Seven blood cultures were taken, all of which failed to show any growth of organisms. Pleural fluid cultured on several occasions failed to show the presence of any organisms. A superficial vein with a very recent thrombophlebitis, and still showing a red streak on the skin, was surgically removed and culture of it by aerobic and anaerobic methods failed to show any organisms. In February and April, 1933, sections of veins were removed for culture and pathological study. The pathological report by Professor Oskar Klotz of the Department of Pathology was as follows:

*"Veins of Leg.*—This specimen of vein was received in February, 1933, when it was removed for bacteriological examination. The tissues proved to be sterile by the various procedures which were undertaken. The vein was a superficial one and was thrombosed at the time of its removal. The sections showed a thin-walled vein which in its surroundings was devoid of an inflammatory reaction but which contained a recent laminated red clot. The clot contained a fair number of leucocytes. The inner portion of the vein wall, including its intima and very narrow zone of the media, showed necrosis with a granular destruction of the tissue elements. There was no inflammatory reaction in this necrotic zone. In the remaining portion of the vessel wall no peculiar features were noted. One was rather struck by the absence of any reaction in the vein wall or in the tissues surrounding it.

*"Diagnosis.*—Phlebitis migrans with thrombosis.

*"Comment.*—The striking feature in this vessel is the absence of an adequate reaction which is usually considered necessary to play a part in thrombosis. In the vessel with the thrombus fully formed, the intima was found to show necrosis

of its elements without any inflammatory response. The thrombus itself was of the usual red, laminated variety, and no peculiar quality was evident in it. It would seem that the vessel wall is not the primary factor leading to thrombus formation. The question arises whether an altered state of the blood could account for the recurring thromboses."

At the time of death, the clinical diagnosis was thrombophlebitis migrans, the thrombosis affecting many of the superficial and deep veins of both arms and legs, the pulmonary veins, and involvement of a coronary vein.

A summary of the autopsy report from the Department of Pathology follows, and we are indebted to Professor Klotz for his particular interest in this case and for his personal opinion after examination of the sections.

#### AUTOPSY REPORT

*Thorax.*—The left thoracic cavity contained 1,000 c.c. of pinkish red, watery fluid, and there were a few fibrinous adhesions at the apex. The right thoracic cavity was almost entirely obliterated by fibrous adhesions but contained about 500 c.c. of similar fluid. The pericardial sac was adherent to the heart, and the wall of the sac was markedly thickened.

On the outer surface of the trachea there were a number of enlarged lymph glands: these were anthracotic and showed the presence of white, firm tissue, suggesting newgrowth. On opening the left main bronchus, it was found occluded by pedunculated, friable, papillomatous masses.

On cutting the lungs it was seen that the pulmonary artery had at various places firm white thrombi attached to its wall. There appeared to be no thrombi in the pulmonary vein. The cut surface of the lung was purplish red, with lobular distribution in scattered areas. The lung was firm and slightly raised above the surrounding tissues.

*Heart.*—The pericardium was attached to the heart by fibrous adhesions. The heart measured 12 by 10 by 4 cm. and weighed about 450 grams. The apex was blunt, and the surface was covered with a small amount of pericardial fat only. Both right and left ventricles were slightly dilated and hypertrophied. The coronary venous sinus, opening into the right auricle, was found to contain a yellow fibrinous mass completely occluding it. None of the remaining vessels of the heart were thrombosed. The myocardium was a good color and showed no evidence of vascular derangement nor fibrosis. Along the upper border of the left auricle and firmly attached to it was a considerable mass of newgrowth infiltrating the loose tissues about the heart and aorta. Some of this growth was present in enlarged lymph nodes. The right ventricle contained many round, white, firm masses. These masses consisted of small smooth-walled lumps of fibrin which had pedunculated attachments to the wall of the ventricle. Some of them lay between the neighboring musculi pectinati. Those attached by a pedicle were very easily dislodged from the point of attachment.

The wall of the left ventricle was free from these thrombotic masses and measured up to 1.5 cm. in thickness. The free border of the mitral valve was slightly thickened with white pinhead-sized nodular masses. The coronary arteries showed several small yellowish plaques in their lumina, but no stenosis was present.

*Microscopic Report.*—The microscopic report on coronary sinus, hypogastric vein, and heart was made by Professor Klotz. (Other veins studied in detail are not reported, but they were essentially the same as the ones described.)

*Coronary Sinus:* Sections were cut of the coronary sinus close to its mouth in the left auricle. At this point the sinus was completely occluded by a recent thrombus composed of a laminated clot. A considerable number of leucocytes were

collected in patches, while in other areas the clot appeared to consist of a granular material. Red blood cells had almost entirely disappeared from the clot. There was no evidence of organization.

*Hypogastric Vein:* This vein showed the presence of an old and a recent lesion. The old lesion consisted of an organized thrombus partially occluding the lumen, while the new lesion was that of a recent red thrombus completely obstructing the vein. The old lesion appeared to be in relation to the structures resembling valves. Numerous pigment-containing cells were seen in the tissues of organization where large numbers of capillaries were found. The adherent red clot showed early proliferation reaction on the part of cells near the surface of the intima, which were extending into the clot itself. As one studied the clotted mass within the lumen, the character of the thrombus suggested different ages to different portions. Parts could be picked out where the thrombus was progressing in the organization and the red blood cells were being destroyed. In other portions such changes were not encountered.

*Heart:* Sections of the myocardium showed normal-looking muscle fibers and an absence of an inflammatory exudate. There was no definite evidence of degenerative changes in the myocardial fibers although there was slight variation in the size of the individual elements. In one section taken near the endocardial surface a mixed thrombus was found lying within the mouth of a sinus. The deepest portion of this thrombus was attached to the wall of the sinus and was undergoing organization. Superimposed upon this was a more recent thrombus, rich in fibrin and containing many leucocytes. The musculature in the neighborhood of the sinus did not appear to be influenced by the presence of the thrombus. There was no degeneration of the muscle fibers.

*Comment on Pathological Study.*—In the various vessels which were examined, and these were all veins save for the pulmonary artery, thrombosing processes of varying ages were encountered. In many cases the vessel wall showed little reaction which could be associated with the presence of thrombus. In the pulmonary arteries, an acute reaction was found in the intima and media. These responses, as well as the hemorrhage about the artery, were often related to the presence of cancerous metastases within the lymphatic channels. This cancer arose in the bronchus. In the femoral artery, a chronic nodular phlebitis was encountered, but whether this had any relation to the thrombus is difficult to say.

It would appear from the autopsy findings and the histological study that the thrombosing process was the outcome of changes in the blood itself rather than the result of primary lesions in the vessel wall. The nature of such changes and the manner in which they were brought about is not clear. What part was played by the cancer of the bronchus and its extensions along the lymphatics of the lung is not possible to state, but our experience with a number of lung cancers does not suggest that these tumorous states have, in themselves, any peculiar effect upon the construction of the blood. Bacteria could not be discovered in the vessel walls by cultural methods, and the lesions encountered did not suggest a bacterial infection.

#### COMMENT

This case is of particular interest in that, during the course of the thrombophlebitis migrans, the sudden onset of paroxysmal tachycardia associated with dyspnea led us to make a provisional diagnosis of thrombosis of a coronary vein. At autopsy, complete blocking at the right coronary venous sinus by a thrombus was found. There was no apparent change in the heart muscle as a result of this thrombosis.

There did not appear to be any definite symptoms associated with coronary venous thrombosis. The clinical diagnosis was very speculative and depended on the presence of paroxysmal tachycardia in a patient with widespread thrombophlebitis migrans. The presence of multiple pulmonary artery thromboses and bronchogenic carcinoma may have masked the clinical syndrome of coronary venous thrombosis if there was one present. However, no precordial pain or distress was noted, and there were no electrocardiographic changes. It is obvious that there may have been other causes for the paroxysmal tachycardia, and it was not necessarily associated with the venous thrombosis.

The other point which arises from this case is that a thorough attempt was made to ascertain the cause of the thrombophlebitis migrans by clinical, bacteriological, and pathological study, and, as in many other cases reported, no etiological agent could be discovered. The suggestion of Smith<sup>9</sup> that multiple venous thrombi may be the result of latent malignancy is of interest in this case where bronchogenic carcinoma was discovered at autopsy. However, the incidence of thrombophlebitis migrans is not higher in cancerous patients than in noncancerous patients, and it is, therefore, impossible to state that the bronchogenic carcinoma was of etiological significance.

#### SUMMARY

A case of thrombophlebitis migrans is reported in which there was complete occlusion by thrombus formation of the right coronary sinus, as proved by autopsy. Thrombosis of a coronary vein was diagnosed clinically because of repeated attacks of paroxysmal tachycardia in a patient with widespread migratory phlebitis. No significant electrocardiographic changes were observed. At autopsy there were no changes observed in the myocardium that could be ascribed to coronary venous thrombosis. Careful study of the case by clinical, bacteriological and pathological means failed to show the etiological factor responsible for this case of migrating thrombophlebitis.

We are indebted to Professor Duncan Graham for permission to publish this case report.

#### REFERENCES

1. Briggs, J. B.: Recurring Phlebitis of Obscure Origin, *Bull. Johns Hopkins Hosp.* 16: 228, 1905.
2. Brooks, H.: Diffuse Selective Sclerosis of the Superficial Veins, *Am. J. M. Sc.* 142: 352, 1911.
3. Moorhead, T. G., and Abrahamson, L.: Thrombo-Phlebitis Migrans, *Brit. M. J.* 1: 586, 1928.
4. Ryle, J. A.: Thrombo-Phlebitis Migrans, *Lancet* 2: 731, 1930.
5. Legrand, C.: Subacute Venous Septicaemia, *Rev. de méd.* 42: 169, 1925.
6. Coombs, C. F.: Observations on the Aetiological Correspondence Between Anginal Pain and Cardiac Infarction, *Quart. J. Med.* 23: 233, 1930.
7. Hartfall, S. J., and Armitage, G.: Thrombo-Phlebitis Migrans: A Report of Two Cases, *Guy's Hosp. Rep.* 82: 424, 1932.
8. Campbell, M., and Morgan, O. G.: An Unusual Case of Multiple Thrombosis, *Guy's Hosp. Rep.* 80: 34, 1930.
9. Smith, R. E.: A Case of Latent Carcinoma Causing Multiple Migratory Venous Thromboses, *Guy's Hosp. Rep.* 82: 437, 1932.

## In Memoriam

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GEORGE ELGIE BROWN

**I**N THE death of George Elgie Brown, at the age of fifty-one years, the medical profession has lost a real leader, just as he was approaching the pinnacle of achievement.

His dramatic rise from a general practitioner in the small community of Miles City, Montana (1911-1921), to chief of a section in the Division of Medicine of the Mayo Clinic, had all the elements of true romance and bore eloquent testimony to his exceptional qualities of mind and character.

His clinical research, which in the latter years was concerned chiefly with the field of the peripheral circulation, resulted in many outstanding contributions and his enthusiasm and energy were the sparks which activated many of the younger men throughout the country to carry on further studies in this field.

He was one of the small group which was responsible for the formation of the Section for the Study of the Peripheral Circulation of the American Heart Association and was elected the first chairman of the Section. To the great sorrow of its members, he did not live to preside at the first regular annual session.

Doctor Brown finely exemplified the glory of our guild, the desire to share not only with his close associates but with all humanity the best of his mind, his heart, his personality.

His untimely passing has been a crushing loss not only to his closer associates but to the multitude of his admirers and friends throughout the profession.

E. V. A.

# Society Transactions

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## AMERICAN HEART ASSOCIATION, 1936

The twelfth annual scientific session of the American Heart Association was held on May 12, 1936, at the Hotel Phillips, Kansas City, Mo., with Dr. William J. Kerr as presiding officer. The following program was presented.

### Program

#### **The Coronary Flow in Hearts of Individuals Dying of Cardiac Insufficiency.**

William B. Kountz, M.D., St. Louis, Mo.

#### ABSTRACT

Revival of human hearts after death makes possible important functional studies. These are of more than usual interest when applied to the hearts of individuals dying of cardiac insufficiency and should throw light upon the nature of cardiac failure. Hearts of individuals dying of cardiac disease revive less readily than do hearts of individuals dying of other conditions than heart disease. Detailed studies could therefore not be made upon these hearts.

The total coronary flow of a normal heart whose weight was around 300 gm. was found to average, when perfused, about 812 c.c. per minute. The average flow per gram of heart muscle is about 2.7 c.c. per minute. In younger individuals the flow often exceeded this figure and sometimes equalled 5 c.c. per gram of heart muscle per minute. In the hearts of individuals dying of heart disease the total coronary flow may be greater than normal, especially in hearts where a marked hypertrophy had taken place, but when reduced to the terms of unit weight was found to fall below the level of 2 c.c. per gram of heart per minute. In subjects dying of heart failure the flow ranged from 0.75 c.c. to 1.5 c.c. per gram per minute.

These studies would lead one to believe that there is a danger in the reduction of coronary flow. This zone may be reached by hypertrophy and dilatation of the heart which appear to increase the need for blood, which, except perhaps in the early stages, is not supplied commensurately with the demand. In coronary arteriosclerosis the reduction may be due to disease of the blood vessels. In either case coronary artery inflow measured in terms of cubic centimeters per gram of heart is well below 2 c.c. per gram of heart muscle per minute.

#### **The Pathologic-Anatomical Basis of Cardiac Insufficiency.** Emmerich von Haam, M.D., New Orleans, La.

#### ABSTRACT

The frequently observed lack of striking morphological changes in failing hearts has always been a puzzle to clinical investigators, who have tried to explain the marked discrepancy between pathologic-anatomical and pathologic-physiological manifestations in heart failure with numerous terms such as acute myocardosis (Hyman) or essential myocardial insufficiency (Messinger). Little attention has been paid by most pathologists to the fact that accumulation of pathological changes cannot take place in a similar manner in the heart—the only organ of our body in constant active and rhythmic motion—as in other organs such as liver and kidney, and that cytological changes in the contracting heart muscle fiber will have a different appearance from similar changes in other cells. The necessary

consequence of such considerations, however, must be a different evaluation of morphological lesions in the heart with reference to organic function by a special system of cardiac pathology.

In attempting to investigate the pathologic-anatomical basis of cardiac insufficiency, material of 5,213 consecutive autopsies, performed during the years 1932 to 1935 at the Charity Hospital of New Orleans, has been studied by the author. During this period, 749 patients, or 14.4 per cent of the total number of autopsies, had died with the diagnosis of fatal organic heart disease. A comparison of the etiological and pathological types of heart disease in this series demonstrated hypertrophy as the principal factor in syphilitic, congenital, and hypertensive heart disease, degenerative lesions as the principal factor in toxic, pulmonary, and neuro-hormonal heart disease, and inflammatory lesions as the principal factor in infectious and rheumatic heart disease. The most consistent type of morphological changes in failing hearts was represented by the group of degenerative lesions associated with or superimposed upon cardiac hypertrophy.

**The Relationship of Tachycardia to Cardiac Insufficiency.** Drew Luten, M.D., St. Louis, Mo. See page 435.

**The Dynamic Effect of Acute Experimental Poisoning of the Heart With Diphtheria Toxin.** L. N. Katz, M.D., D. B. Witt, M.D., and E. Lindner, M.D., Chicago, Ill.

#### ABSTRACT

The acute effect upon the cardiac dynamics of injecting diphtheria toxin was studied in dogs. The study was based on records of mean arterial and venous blood pressure and records of the volume and pressure changes of the heart. Electrocardiograms were obtained also. The pressure curves of the various heart chambers (i.e., the two ventricles, the pulmonary artery, and the aorta) were recorded with Wiggers' manometer on a photokymograph. The volume and mean pressure curves were obtained on a smoked drum.

It was found that the diphtheria toxin, after preliminary acceleration, produced a sinus slowing of the heart, and later, various types of A-V and intraventricular block. Extrasystoles of various types and paroxysmal tachycardia also were present, and eventually the heart went into a peculiar type of ventricular fibrillation. A vasodilatation in both the systemic and the pulmonary circuits also resulted. Heart failure was caused by these disturbances in conduction and rhythm, and by the decreased coronary blood supply following systemic vasodilatation. There was definite evidence, however, that diphtheria toxin poisoned the heart in such a way that myocardial failure with its typical abbreviated and less powerful contraction occurred before these other changes came into operation. It is of practical importance to realize that diphtheria toxin acts directly on the contractile power of the heart since serious damage to the heart may be present without significant modification of the electrocardiogram or of blood pressure and heart rate.

**Cardiac Asthma (Paroxysmal Dyspnea) and Failure of the Pulmonary Circulation.** Soma Weiss, M.D., and George P. Robb, M.D., Boston, Mass.

#### ABSTRACT

Failure of the pulmonary circulation frequently develops independently of failure of the greater circulation. Cardiac asthma (paroxysmal dyspnea) results from acute and usually transient hypertension within the pulmonary circuit. The most frequent cause of attacks is acute or subacute left ventricular failure.

As indicated by clinical symptomatology, by circulatory measurements and by responses to chemical agents, there are three types of paroxysmal cardiac dyspnea which may occur singly or combined: (1) simple paroxysmal dyspnea without evi-



dence of bronchial spasm or intra-alveolar edema; (2) paroxysmal dyspnea with bronchial spasm and true asthmatic breathing; (3) paroxysmal dyspnea with intra-alveolar edema.

As judged from histological examination of the lungs, fatal paroxysmal cardiac dyspnea may occur without an appreciable degree of intra-alveolar edema, but with pericapillary edema. In this type of edema the tissue fluid is localized mainly between the capillary and alveolar basement membranes, but does not penetrate the alveolar basement membrane or the epithelial layer of cells. Hence the alveolar space contains no fluid. Such lungs may be heavy. In instances in which paroxysmal cardiac dyspnea is associated with true asthmatic breathing, there is sensitivity to histamine, and clinical improvement follows the administration of epinephrine. There are also instances of paroxysmal dyspnea regularly associated with diffuse intra-alveolar edema. This type is likely to occur in patients with advanced ("tight") mitral stenosis and in patients with arterial hypertension and uremia in whom osmotic pressure of the serum is low. Recognition of these types of pulmonary reaction in paroxysmal cardiac dyspnea bears on the therapy of this condition.

**Cardiac Insufficiency in Coronary Thrombosis.** Arthur M. Master, M.D., Simon Daek, M.D., and Harry L. Jaffe, M.D., New York, N. Y.

#### ABSTRACT

The rôle of cardiac insufficiency and related factors in the course and prognosis of 140 attacks of coronary thrombosis was studied. Congestive heart failure was more frequent in the older age groups and in those with a previous occlusion, hypertension, or enlarged heart. It developed in two-thirds of the cases and was usually combined left and right, although the lesion primarily involves the left ventricle alone.

The heart failure was classified as left or right on the basis of clinical signs and symptoms, venous pressure, circulation times and vital capacity. The latter proved a simple accurate measure of heart failure. The prognostic significance of tachycardia, low pulse pressure, poor heart sounds, gallop rhythm, tachypnea, orthopnea, pulmonary edema, cyanosis, fever, leucocytosis, hypertension, and cardiac enlargement was evaluated. Shock and congestive failure frequently occurred simultaneously.

Arrhythmias, though they tended to aggravate shock and heart failure, were transitory and required no specific treatment.

Heart failure increased the mortality rate. It was present in all but two of the thirty fatal cases and occurred equally in anterior or posterior infarction and in left or right coronary occlusion; more than one vessel was nearly always occluded; an old thrombosis was present in the majority, and the left coronary artery was usually initially involved.

**The Differential Diagnosis of Congestive Heart Failure and Constrictive Pericarditis (Pick's Disease).** Howard B. Sprague, M.D., Boston, Mass. See page 443.

**Studies on the Effect of the Action of Digitalis on the Circulation in the Presence of Congestive Heart Failure.** Harold J. Stewart, M.D., J. E. Deitrick, M.D., and N. F. Crane, M.D., New York, N. Y.

#### ABSTRACT

Studies of the effect of giving digitalis on the circulation have been made in patients exhibiting the signs and symptoms of congestive heart failure. Patients suffering from heart disease of rheumatic etiology, as well as those exhibiting

arteriosclerosis and hypertension, were included; in each etiological group there were patients exhibiting normal sinus rhythm as well as those in whom the rhythm was auricular fibrillation.

All observations were made with patients in a basal metabolic state. Observations were made first immediately before digitalis was given and later twenty-four hours after digitalis, 1.8 gm. (A.H.A. preparation), had been given by mouth, and then again at intervals later still. Records were made of the heart rate, of electrocardiograms, of arm-to-tongue circulation time (decholin), of venous pressure (direct methods), of cardiac output (acetylene method—3 sample technic), of size of heart (x-ray photographs of heart taken at a distance of 2 m.). In the patients who were observed, the giving of digitalis was associated with *decrease* in cardiac size, *decrease* in circulation time, *increase* in cardiac output, and *lowering* of venous pressure if it was elevated. The work of the heart before digitalis was given was not commensurate with the size, but following the administration of digitalis, the work accomplished at each beat became greater and more nearly commensurate with the size of the heart.

**Inhibiting Thyroid Activity in the Treatment of Cardiac Insufficiency: A Report of Four Cases.** James A. Lyon, M.D., and Edmund Horgan, M.D., Washington, D. C.

#### ABSTRACT

Four cases of cardiac insufficiency are reported in which improvement followed the devascularization of the thyroid gland to inhibit thyroid activity. In one case improvement has now been maintained for twenty-two months. This patient, who prior to operation worked with difficulty, is able to work regularly from ten to twelve hours a day without discomfort. His systolic blood pressure which formerly ranged from 150 to 300 mm. of mercury has now become stabilized at 140 mm. In another case improvement has been maintained for twelve months. This patient prior to operation was partially incapacitated for five months; since operation she has been able to work regularly for six to seven hours daily. Two patients have died. Both showed definite early improvement. One who had resumed work after having been incapacitated for three years prior to operation died of mesenteric thrombosis five months following operation. The other died of cardiac insufficiency twenty-two months following operation. With the exception of the last-mentioned patient, none has had a recurrence of cardiac insufficiency.

On the basis of the results obtained by the operation of devascularizing the thyroid gland to inhibit thyroid activity, the authors conclude that the method utilized by them has a place in the treatment of patients having cardiac insufficiency.

#### SECTION FOR THE STUDY OF PERIPHERAL CIRCULATION

**Hemiconstriction of Vascular System Associated With Cerebral Disease.** William J. Kerr, M.D., and F. J. Underwood, M.D., San Francisco, Calif. To appear in an early issue of this JOURNAL.

**The Control of Sympathetomized Blood Vessels by Sympathomimetic Hormones and Its Relation to the Surgical Treatment of Raynaud's Disease.** James C. White, M.D., Boston, Mass.

#### ABSTRACT

In line with the behavior of unstriated muscle in general, denervated smooth muscle in the arterial walls becomes abnormally sensitive to circulating sympathomimetic hormones as the vasoconstrictor nerves degenerate. The increase in sensitivity is much greater after degeneration of the postganglionic neurones than

after destruction of the preganglionic portion of the vasoconstrictor pathway. This has been measured in the rabbit's ear and the monkey's hand, as well as in human extremities. The most important hormone which mediates residual vasospasm in denervated arteries appears to be adrenalin. Sympathin and other, as yet unknown, substances probably play a contributory rôle. In explanation of the inferior results of cervicothoracic ganglionectomy, we have shown that this operation causes a degeneration of the postganglionic fibers to the brachial plexus, and thereby a maximal tendency to residual vasospasm during exposure to cold, exertion, or emotional stress. In contrast, lumbar ganglionectomy interrupts the vasoconstrictor outflow to the sciatic nerve in its preganglionic portion, and thereby leaves a minimal residual response to chemical stimuli. Application of these principles to the treatment of Raynaud's disease in the upper extremity is leading to a more physiological operation in which the ganglia giving rise to the postganglionic neurones are preserved, but the preganglionic connections are cut proximally. This method promises to give as favorable results in the arm as have been achieved in the leg.

**Modified Dorsal Sympathectomy for Raynaud's Disease (Vascular Spasm) of the Upper Extremity.** R. H. Smithwick, M.D., Boston, Mass.

ABSTRACT

In contrast to the excellent results which for years have been obtained from lumbar ganglionectomy for vascular spasm (Raynaud's disease) of the lower extremity, the results from a similar procedure; namely, cervicodorsal ganglionectomy, for Raynaud's disease of the upper extremity have been very unsatisfactory in our experience.

Extensive study of the anatomical and physiological considerations involved have led us to believe that it is possible to obtain satisfactory results in the upper extremity. A series of cases is presented in which a modified dorsal sympathectomy has been employed in order to sympathectomize the upper extremity. In this operation only preganglionic fibers are divided, and no ganglia are removed. A follow-up study of about twenty-five extremities over periods of a few weeks to over a year makes us feel that this operation will prove to be satisfactory.

One cannot speak too dogmatically about the results as yet until another year or so has passed. The chief cause of failure in the operation of ganglionectomy was probably due to sensitization of the blood vessels to circulating hormones, which cause residual vascular spasm after degeneration of postganglionic neurones. Adrenalin is probably the most important of the hormones in question.

If regeneration of nerve fibers does not take place, the operation should prove to be of considerable practical value.

**Studies on the Nature of the Peripheral Resistance in Arterial Hypertension.**

Myron Prinzmetal, M.D., Los Angeles, Calif., Ben Friedman, M.D., New York, N. Y., Clifford Wilson, M.D., London, England.

ABSTRACT

Determinations of resting blood flow in the arm in various types of hypertension give an average value no greater than that obtained from subjects with normal blood pressure. This indicates that increased vascular resistance in the different types of hypertension is not confined to the splanchnic area but is generalized throughout the systemic circulation. Patients with hypertension show increase in blood flow in response to heat and reactive hyperemia equal in degree to that produced in normal individuals, showing that the blood vessels in hypertension are capable of considerable dilatation and indicating that the increased peripheral resistance is due to hypertonus and not to organic changes in the vessel walls. Sympathetic vasodilatation produced by the "heat test" produces no greater in-

crease in blood flow in subjects with high blood pressure than in normal individuals, suggesting that the vascular hypertonus is not vasomotor in origin. Patients with coarctation of the aorta, on the other hand, show a greater increase in blood flow in the arm in response to the heat test than do controls or patients with generalized hypertension. This demonstrates that vasoconstriction of sympathetic origin is present in the upper extremities in coarctation of the aorta and affords confirmatory indirect evidence that the hypertonus in generalized hypertension is not of vasomotor origin. Anesthetization with procaine hydrochloride of the vasomotor nerves to the arm produces the same increase in flow in normal subjects and patients with hypertension, proving that the vascular hypertonus is independent of the vasomotor nerves and that this hypertonus must therefore be regarded as intrinsic spasm of the blood vessels themselves. These conclusions apply to all types of hypertension, and hence there is no physiological evidence for the separation into "organic" and "functional" types or for the assumption that renal hypertension is due to vasomotor hypertonus. Surgical procedures aiming at the relief of high blood pressure by sympathectomy do not abolish the vascular hypertonus that is fundamentally responsible for the hypertension.

**Anterior Nerve Root Section and Splanchnic Section in the Treatment of Hypertension.** Irvine H. Page, M.D., New York, N. Y.

#### ABSTRACT

Since no treatment of medical nature is known which will lower arterial blood pressure more than temporarily in patients suffering from essential or malignant hypertension, surgical measures have seemed worthy of trial. The purpose of this investigation was to compare and ascertain the merits of anterior nerve root section and resection of the splanchnic nerves. (The operative procedures have been carried out by Dr. George Heuer at the New York Hospital.)

Favorable results have been considered marked and persistent lowering of blood pressure, regression of morbid eyeground changes, disappearance of subjective symptoms, and often decrease in the size of the heart. Our results may be grouped as follows as regards the outcome which may be expected from operation: (1) those patients in whom the disease is benign and in whom advanced vascular change has not occurred may respond well; (2) in those more advanced cases of long standing with morbid vascular change but benign in character, a favorable result may be obtained by no means certainly; (3) young patients, exhibiting hypertension bordering on the malignant variety and exhibiting symptoms and signs of the "diencephalic syndrome," may respond in a satisfactory manner; (4) patients suffering from highly malignant hypertension are far less likely to respond favorably.

In some of the cases relief has been dramatic; in others, especially those with highly malignant hypertension, operation has not appeared to influence the course of the disease. However, since two of five such cases were markedly benefited, operation may be worth a trial.

Nine patients have had supradiaphragmatic splanchnic resections performed. In all of the patients but two the disease was benign. Of the two, one was highly malignant and the other had marked reduction of renal efficiency. The results of this operation have been disappointing except in two of the very benign cases. Some reduction of pressure occurred in them, but it is too early (five months) to be certain that the pressure will not again rise. The remainder of the patients were not helped by operation.

**A New Method for Determining the Circulation Time Throughout the Vascular System.** Lester C. Spier, M.D., Irving S. Wright, M.D., and Leslie Saylor, M.D., New York, N. Y. To appear in an early issue of the JOURNAL.

**Thorotrast Arteriography in Vascular Diseases of the Extremities, With Report of Illustrative and Unusual Cases.** Wallace M. Yater, M.D., Washington, D. C. See page 383.

**Sudden Arterial Occlusion in Thromboangiitis Obliterans.** Walter F. Kvale, M.D., and Edgar V. Allen, M.D., Rochester, Minn. See page 458.

**Ischemic Pain in Exercising Muscle: Its Nature and Implications.** A. H. Elliot, Jr., M.D., and Richard D. Evans, M.D., Santa Barbara, Calif. To appear in an early issue of the JOURNAL.

**Observations on Intermittent Claudication—Response to Treatment Measured Graphically.** Lewis H. Hitzrot, M.D., Philadelphia, Pa.

#### ABSTRACT

The abnormal fatigue which occurs during contraction of the calf muscles deprived of adequate blood supply can be recorded graphically. In this study the variables due to voluntary control of the muscle contraction have been eliminated. The muscle group is stimulated electrically over fixed periods at varying frequency. A pen records the excursion of the foot extended with each stimulation; rest periods are so spaced to show recovery or lack of it after fatigue has been produced.

The presentation offers data from a study of the objective changes recorded by patients with suspected or proved vascular disease. Their fatigue curves show definite degrees of variance from normal standards which may aid in diagnosis and prognosis.

Comparison of the fatigue records of the same patient before and after treatment as with alternative suction and pressure or with injections of tissue extract, allow objective evaluation of such treatment. The fatigue curves have proved of value in cases in which the symptoms are equivocal or in which clinical evidence of progress under treatment is uncertain. Reproductions of individual and composite curves illustrate the clinical possibilities of the procedure.

#### DISCUSSION\*

**Discussion of the paper, "Coronary Flow in Hearts of Individuals Dying of Cardiac Insufficiency," by Dr. Kountz.**

*Dr. Fred Smith, Iowa City, Iowa.*—Dr. Kountz has done some remarkable things with revived hearts. I doubt very much, however, if we are justified in drawing definite conclusions from the results reported. In the first place, the perfusion method is not a very satisfactory way of studying the coronary circulation in terms of absolute amounts. Moreover, we have no idea as to the extent of changes in metabolism which may have taken place in these hearts. The physiologists in recent years have demonstrated, among other things, that asphyxiation and reduction in the coronary circulation have a pronounced influence on the glycogen content of the myocardium. It is reasonable to assume that this must have a significant influence on the function of the heart.

*Dr. Samuel Shelburne, Dallas, Texas.*—I should like to ask Dr. Kountz if he has been able to make any observations during these experiments on oxygen utilization per gram of muscle weight, which might have some bearing on the things mentioned by Dr. Smith.

*Dr. Kountz.*—One certainly admits Dr. Smith's statements. These facts were made plain in the paper. The fact that one can revive hearts that have died, can

\*The discussion of the papers presented before the Section for the Study of the Peripheral Circulation was not recorded.

make them beat, and carry normal blood pressures over periods of hours indicates that anoxemia and asphyxia probably do not play so much a part as one might suspect. Of course, in hearts of individuals dying of heart disease one deals with a somewhat different condition. These latter organs have been subjected to chronic asphyxia over a longer period, and chemical changes have occurred which are difficult to reverse.

Study of the coronary flow by oxygen utilization in these hearts has not been attempted. The method perhaps should serve as a check on our present work.

Discussion of the paper, "The Pathologic-Anatomical Basis of Cardiac Insufficiency," by Dr. von Haam.

*Dr. L. L. Bresette*, Kansas City, Mo.—How often do you find similar changes in hearts that do not present any clinical picture?

*Dr. Simon Dock*, New York, N. Y.—How often do you find no organic change in hearts which have failed?

*Dr. von Haam*.—In the study of 700 failing hearts I have never failed to find organic changes. The purpose of this study has not been to lay down strict rules of pathology concerning cardiac insufficiency but to demonstrate to you that all principal pathological lesions encountered elsewhere in the body during disease and associated with loss of organic function are also present in the failing heart. In order to correlate those morphological changes with loss of cardiac function resulting finally in cardiac failure and perhaps cardiac death, we have to use a different system of evaluation since the heart does not show accumulation of pathological changes in a degree similar to that found in other organs of the body.

Discussion of the paper, "The Relationship of Tachycardia to Cardiac Insufficiency," by Dr. Drew Luten, St. Louis, Mo.

*Dr. L. N. Katz*, Chicago, Ill.—Several questions are brought up by this interesting and challenging communication. A moment's reflection and an assay of the literature show that a fast heart is a much less efficient organ than a slow one. This is so for a number of reasons. In the first place, a fast heart has not as much time to recover as a slow one and is thus in a less rested state. In the second place, the heart is a poorer energy machine when it is beating rapidly than when it is beating slowly. In other words, it does less work for the same amount of energy.

In the third place, as Dr. Wiggers and I have shown, the distribution of the power of the heart is disadvantageously distributed in a rapid heart. To insist, therefore, that a rapid heart is a compensatory mechanism for the inadequacy of output gives a wrong impression of the efficacy of the circulation. It is generally conceded clinically that the prognosis is better for immediate relief of the failure when the heart is rapid than when it is slow. Obviously, this is so since when the heart is rapid, it can be slowed.

Furthermore, digitalis acts primarily to improve the efficiency of the heart. Dock has presented good evidence, some unpublished, which our work seems to confirm, that the action of digitalis may not be on the heart alone but on the venous return to the heart produced by narrowing of the venules, particularly those of the liver. Decreasing the amount of blood coming to the heart decreases its distention and so leads to the improvement. The action of digitalis on the heart is primarily on the conductivity of the impulse, particularly on the A-V node, and to a lesser extent on the irritability and responsiveness of the ventricles.

It is hazardous to dismiss the old point of view that tachycardia is a detrimental factor and substitute the view that it is a beneficial one. The converse is still the

opinion of most cardiologists. Thus, it is known that congestive failure may follow paroxysmal tachycardia in patients with organic heart disease.

*Dr. Luten.*—I hardly knew whether I was needlessly defending a point of view which has come generally to be held or offering something radically different. Dr. Katz has been kind enough to set me straight on that. The theory that the beneficial effect of digitalis lies wholly in its slowing effect is credited to Mackenzie, but Mackenzie was careful never to state that benefit is due entirely to slowing. It is true that any considerable degree of slowing occurs only in cases of fibrillation. That is the thing which attracts attention and which is easiest to measure; and the early conclusion was that improvement is due to slowing. Sir Thomas Lewis has insisted that reduction in rate is the only mechanism by which digitalis improves heart failure. You know better than that; you know that cases of heart failure improve after digitalis whether they have fibrillation or not, whether slowing occurs or not. You know that digitalis does have an effect on the heart muscle, whatever effect it may have on the conducting tissues.

I do not mean for a moment to deny that digitalis lessens conductivity. It is extremely difficult to prove it. If the auricle sends an impulse to the ventricle and one can measure the interval elapsing until ventricular response, I know of no proof that that interval represents only transmission time. I have no doubt, however, that digitalis does lessen conductivity. The point I am trying to make is that in view of the well-known effect of the drug on the muscle, we have centered attention too much on its action on the A-V tissues.

I did not have the time to refer you to work showing that in heart failure digitalis lessens ventricular irritability. It would appear only logical to assume (particularly with good physiological evidence) that impulses may reach the ventricle and not excite it. It is illogical not to take into account this lowering of ventricular irritability in heart failure as a prominent cause of the slowing.

If by its muscular action digitalis causes improvement in cases of heart failure with normal rhythm, will it not have the same beneficial effect on the ventricular muscle in the case of such a patient with an auricular circus movement? Must not at least a part of the improvement in patients with failure and fibrillation be due to the effect of the drug on the muscle, the same as in other patients with failure? After demonstration of the fact that in congestive failure the muscular effect of digitalis is such as to cause improvement, why disregard entirely this well-known effect of the drug on the muscle and say that in cases with auricular circus movement the improvement is due to something else? Agents other than tachycardia are well recognized as causes of heart failure; relief need not depend on slowing.

One thing more: There is no obligation for one always to try to slow a tachycardia, whether it is associated with fibrillation or not. It becomes less and less a therapeutic objective. One used to try to induce slowing in a pneumonia patient with tachycardia. Attention now is directed elsewhere: if the patient improves, the rate declines. If a patient with heart failure gets better, his tachycardia subsides whether he has fibrillation or not.

#### Discussion of the paper, "The Dynamic Effect of Acute Experimental Poisoning of the Heart With Diphtheria Toxin," by Drs. Katz, Witt, and Lindner.

*Dr. A. R. Barnes, Rochester, Minn.*—Mr. Chairman, I think we are greatly indebted to Dr. Katz and his coworkers for this excellent piece of work. I think he is right in diverting our attention from disturbances of conduction as a manifestation of diphtheritic infection of the heart. I thought Dr. Nathanson was here, and I hoped he would have a word to say because he has done some excellent work on this subject and he was one of the first men who called my attention to the fact that the T-wave changes were produced in the electrocardiogram in patients

sick with diphtheria independent of conduction disturbances. He amplified this work still further and reproduced the work experimentally in cats. He also pointed out to me the fact that in his experience the patients who had the T-wave changes in the course of their illness, even though they appeared to be getting along in excellent shape, not infrequently suddenly died and it became his custom when these T-wave changes appeared in the electrocardiogram to be unusually cautious in keeping these patients at bed rest for a long period of time. I think we ought not to neglect to give Dr. Nathanson the credit for having called our attention to this particular phenomenon.

*Dr. M. H. Nathanson, Minneapolis, Minn.*—I wish to point out that the results which Dr. Katz obtained in his experiments may not be applicable to clinical diphtheria. I do not believe that Dr. Katz intended to leave the impression that the acute poisoning which he produced necessarily represents the conditions which exist in the heart in diphtheria. I studied a group of diphtheria patients through convalescence and found marked electrocardiographic changes not uncommon, especially if the toxemia had been severe. These patients showed no signs of cardiac insufficiency. There may have been some disturbance in the dynamics of the heart, but this could not be detected clinically.

In clinical diphtheria the electrocardiographic modification may be, and usually is, the only indication that the myocardium is involved. An impairment in the contractile power of the myocardium sufficient to produce symptoms is rare, and when this occurs the electrocardiogram has already shown significant abnormalities. Death is usually sudden, without the development of symptoms and signs of decompensation.

*Dr. Drew Luten, St. Louis, Mo.*—Mr. Chairman, it occurred to me when Dr. Katz was reporting his extremely important work that it probably is another illustration of the viewpoint I tried to emphasize, that is, that the important thing is the effect on the whole muscle, rather than on such a small part of the muscle as the A-V bundle. His curve showed, if I followed him correctly, that there was evidence of ventricular impairment before conduction changes or rhythm changes were observed; and it struck me as a possibility, maybe a probability, that this very effect on the ventricle was the thing that produced the prolongation in A-V time, the muscle being involved, perhaps as much as the A-V tissues, in the exhibition of changes in the P-R interval.

*Dr. William J. Kerr, San Francisco, Calif.*—I would like to ask Dr. Katz a question. We know that the French use ouabain a good deal in patients following attacks of diphtheria, and I wonder if Dr. Katz has tried such substances on hearts studied to see what the result is in controlling the efficiency of the myocardium.

*Dr. Katz.*—In regard to myocardial changes, we have made some sections of these hearts, and the pathologist reports that there is nothing to see other than cloudy swelling, no hemorrhages, no evidence of necrosis. Our experiments were acute and not chronic, a fact which might not permit time for the development of morphological or histological effects. In chronic experiments, such as those of Dr. Nathanson, and in clinical cases, necrosis has been described. In other words, our effects were based on functional and not morphological effects.

I am grateful to both Dr. Barnes and Dr. Nathanson for their discussions, because I had no intent at all of ignoring the literature. Dr. Nathanson and I have discussed this problem several times, and I am well aware of his results. I think he is the first to have pointed out clearly that aside from conduction disturbances one should look for changes in the configuration of the ventricular complex.

I just want to rectify one statement that Dr. Nathanson made. We did not have evidence of congestive heart failure. We did find a rise in venous pressure on either



the right or left side. These are acute effects in animals and are important in that such acute effects may also occur suddenly in patients with diphtheria.

As regards Dr. Luten's discussion, there is no question that digitalis toxin and other poisons act on all the properties of the heart. The point is, which of the effects are dominant? Our results show that in spite of the slowing, the power of the heart goes down and not up.

We have had no experience with ouabain.

Discussion of the paper, "Cardiac Asthma (Paroxysmal Dyspnea) and Failure of the Pulmonary Circulation," by Drs. Weiss and Robb.

*Dr. A. A. Getman*, Syracuse, N. Y.—I should like to ask Dr. Weiss the reason for the paroxysmal character of the dyspnea. I understand quite fully, I think, why the patients have dyspnea, but I do not understand why it should occur in the evening, why we see it so often occurring at night, and why it is paroxysmal. Why do these patients not have dyspnea all the time?

*Dr. Weiss*.—If Dr. Kerr will permit me, I should like to answer that question in a little more detail. I purposely omitted that very important point because we had studied it previously and had already reported our experience.

I have tried to take up a few points bearing on the lungs only because I wished to emphasize that, in my opinion, the term "cardiac asthma" is a good one since it calls attention to the fact that there is not only a cardiac but also a pulmonary element. However, in cases of pure cardiac asthma, the heart is the primary trigger mechanism. It is in connection with this trigger mechanism that the question asked comes up, namely, "Why do attacks come on in paroxysms and why do they occur mainly at night?" First of all, they do not necessarily come on at night but may occur during the day, especially in advanced cases. On the other hand, it is true that a patient may be able to do his work in the daytime and then at night may develop serious attacks. We believe the reason for this is as follows: These patients, as I mentioned, have some pathology in the left ventricle which is just on the borderline of failure. Even if they are in a high pillowed position when they go to bed, very often during the night they gradually slide down. This lowered position of the lungs predisposes to pulmonary edema. We have actually observed patients whom we have placed in Gatch beds. After they were asleep, we have lowered the head of the bed and listened for pulmonary signs. At the base of the lungs we could hear râles develop. Then, while the patient is still in bed, for some reason the blood pressure becomes rather suddenly or gradually elevated. This may be brought about by a distended bladder, a desire to defecate, a night dream, or a great many other factors. Thus while the lungs are filling up, the arterial pressure suddenly becomes elevated. At this time the left side of the heart begins to fail and blood is trapped in the pulmonary circuit. The patient then wakes up, often with a feeling of distress or fright. This, of course, further increases the failure of the left ventricle. Failure may occur in the course of a few minutes, so that the pulmonary circuit becomes overfilled and distended.

The patient will get better in one of two ways: Improvement may occur spontaneously since, if the patient stays in bed, he may go into collapse or shock, producing a failure of the peripheral circulation which acts as a venesection. Thus, just when we think the patient's condition has become desperate, he begins to improve.

The second method of improvement is one commonly observed. The patient will tell you, "I have to rush to the window" or "I have to go to the bathroom to brush my teeth." Whatever bodily change causes the relief, it is always associated with an orthostatic position, although the patient does not know why he has a desire

to get up, to stand by the stairs, or to go to a window. As the patient stands, a certain amount of blood is pooled in the peripheral circulation and that relieves the pulmonary circulation.

Almost all the therapeutic measures which are successful in paroxysmal cardiac dyspnea are effective because they pool blood in the peripheral circulation from the pulmonary circulation, or because they overcome certain vasospastic reflexes, thus accomplishing the same thing.

In conclusion, in answer to this specific question, we believe that in cardiac asthma we are dealing with patients with borderline failure of the left ventricle. In addition, I wish to emphasize again that these patients have a reduced reserve of the pulmonary capillary bed. This capillary bed cannot distend; hence a small amount of blood trapped in the pulmonary circulation by the factors mentioned, either at night or during the day, will be enough to set up the sequence of events described.

Discussion of the paper, "Cardiac Insufficiency in Coronary Thrombosis," by Drs. Master, Dack, and Jaffe.

*Dr. M. H. Nathanson, Minneapolis, Minn.*—Dr. Master and his associates find a very high incidence of cardiac insufficiency associated with coronary thrombosis. I wish to point out that these figures are applicable only to the group which was studied, a group of hospitalized patients. If an analysis is made of a more general group, such as a series from a pathological department, the incidence of cardiac insufficiency is much lower, especially if the cases from the coroner's service are included. In an analysis of 113 autopsies of acute and chronic occlusive disease of the coronary arteries, I found that cardiac insufficiency as indicated by clinical symptoms and by passive congestion of the liver at autopsy, was present in but 42 per cent. In 58 per cent, death was sudden, and there was no evidence of cardiac insufficiency in the clinical history or in the autopsy findings.

I also found that cardiac insufficiency was far more frequent in coronary disease when the heart was enlarged. In 45 autopsies in which the heart weight was 400 gm. or less, cardiac insufficiency was present in only 7 per cent, while sudden death without cardiac insufficiency occurred in 93 per cent. In 68 autopsies in which the heart weight was above 400 gm. ranging from 450 to 600 gm., cardiac insufficiency was present in 63 per cent while sudden death without cardiac insufficiency occurred in 37 per cent.

*Dr. Daniel J. Glomset, Des Moines, Iowa.*—I want to make one comment on this interesting work; namely, that I do not believe it is possible to call any attack of coronary thrombosis or any attack of a myocardial infarct an initial one. From my own experience in dealing with somewhere around 100 of these cases, I believe there are a large number of these coronary infarcts which are asymptomatic, so much so that I presume that when symptoms are present, it is the second or third attack and not the first.

*Dr. Howard B. Sprague, Boston, Mass.*—I would like to point out in connection with this correlation between left ventricular failure and combined right and left ventricular failure, that, in coronary occlusion, we are dealing with a very diffuse involvement of the coronary circulation, involving both sides, and that the work which has just been done in our clinic by Dr. White and our associates has shown that next to mitral stenosis the most common cause of right ventricular failure is failure of the left ventricle. That is, after mitral stenosis, the greatest cause of enlargement of the right side of the heart is failure of the left. So that in the course of failure of the left ventricle in coronary occlusion involving the left ventricle, one would expect that the strain of this failure would be reflected very frequently in failure of the right ventricle, which often has also an inadequate coronary circulation due to the diffuse coronary sclerosis.

*Dr. Fred M. Smith, Iowa City, Iowa.*—I wish to stress the point raised by Dr. Nathanson; viz., that one is likely to get the wrong conception regarding the outlook in coronary occlusion from this paper. During the past few years a more optimistic viewpoint has developed concerning the prognosis of this condition. The analysis of any large series of coronary artery disease will disclose that a fairly high percentage have had a major coronary accident, and yet many of these will have recovered with quite satisfactory cardiac function even though the history oftentimes indicates that the patient is permitted to be up and about the next day or even a few days.

There have been relatively few instances of high grade cardiac failure during the acute stage of coronary occlusion at the University of Iowa. This perhaps may be due to the fact that our patients come from all parts of the state and many travel a considerable distance. Under these circumstances the more acutely ill patients are probably retained under the care of the family physician. Acute left ventricular failure is rather common immediately following cardiac infarction, but this is often a transient condition.

*Dr. L. N. Katz, Chicago, Ill.*—I am sure that Dr. Dack will assure us that these precise measurements were not needed to tell whether their patients had congestive failure or not. It is a bit hazardous routinely to subject patients with acute coronary thrombosis or occlusion with myocardial infarction to some of these tests. Further, it has been stated by a number of workers that the saccharin method and more particularly the ether method sometimes leads to serious complications. I would like Dr. Dack to report on their experience with this method. Have they had any fatalities and untoward reactions with these particular methods? These are not criticisms of the research, but simply made to prevent too much enthusiasm in using these methods routinely. There are only two laboratory methods which help the clinician routinely; one is the electrocardiogram, and the other is the sedimentation rate of the red blood cells.

*Dr. A. R. Barnes, Rochester, Minn.*—I should like to ask the essayist if he has any impression that involvement of the septum of the heart, particularly if it is extensive, played any predominant part in determining the occurrence of congestive failure. I am saying this because I have had a few experiences lately that lead me to suspect that infarction that involves the septum of the heart extensively has a much more important part in determining the occurrence of failure than an equal amount of infarction situated elsewhere in the heart.

*Dr. Dack.*—I would like to take up Dr. Smith's point first. We did not intend to paint a pessimistic picture of the outcome of coronary thrombosis. In fact, only recently we reported the results in a large series of cases. In more than 250 cases of coronary thrombosis the total mortality rate was only 16 per cent, which is much lower than the rates quoted in the literature. The mortality rate in the initial attack, as closely as we could determine, was only 8 per cent. We are thus not very pessimistic about the outcome of coronary thrombosis. All we tried to show was that when death did occur, cardiac failure was usually present.

In answer to Dr. Nathanson, we used ward patients because they could be subjected to much more accurate study. We included in this series all deaths, whether they occurred one minute or two months following admission. We have thus included all the sudden deaths in this series.

There were two sudden deaths among the thirty fatal cases, and these cases did not show cardiac insufficiency at clinical or post-mortem examination. One of these patients died of rupture of the left ventricle and the other of a convulsive seizure, cause unknown. All the other twenty-eight patients showed severe left and right cardiac insufficiency.

Concerning initial attacks, I think we were very careful in searching for a history of a previous attack. Of course, some closures are silent, and the presence of a previous thrombosis can be determined only at post-mortem examination. The majority of the hearts in the fatal cases show more than one closure.

Dr. Sprague's point about the cause of right ventricular failure is just the point that we tried to make. We never observed right ventricular failure alone; it usually followed left ventricular failure, and we think it was due to the severe strain put on the right ventricle following failure of the left.

We never observed a fatality following the determination of the saccharin or ether circulation time, although there have been one or two reports of fatal cases following the use of ether. However, in using saccharin one must not inject outside the vein, otherwise there is a very severe local reaction with much pain. We do not advocate these tests for routine use in diagnosis of cardiac insufficiency. We think that their main value lies in research study. We agree with Dr. Katz that most of our diagnoses could have been made without these tests.

One more point is that in most cases we can obtain as much information from the simple determination of the vital capacity as from the arm-to-tongue circulation time. In most cases it was a more delicate test of cardiac insufficiency than the other circulatory measurements. It was very valuable in following the course of a patient ill with coronary thrombosis. It is usually low after the closure, and, as the patient improves, it gradually rises. If the patient gets well, the vital capacity usually returns to normal.

Twenty-two of the thirty patients who died came to post-mortem examination. Of these, eleven showed gross infarction of the septum, whether the left or right coronary artery was occluded. All of these patients except one had signs of severe right ventricular failure in addition to left. The one exception died in pulmonary edema without signs of right ventricular failure. The eleven other patients, however, developed left and right ventricular failure even in the absence of septal infarction. Investigators like Fishberg think that when infarction of the septum occurs, right ventricular failure almost always follows. Libman has made the observation that signs of rapidly appearing right heart failure a few hours after a thrombosis indicate septal infarction.

Discussion of the paper, "The Differential Diagnosis of Congestive Heart Failure and Constrictive Pericarditis (Pick's Disease)," by Dr. Sprague.

*Dr. William J. Kerr*, San Francisco, Calif.—I should like to ask Dr. Sprague about the specific gravity of the fluid in the chest and in the abdomen in such cases. How often does he find a high specific gravity? And what significance does he attach to this finding?

*Dr. Stewart R. Roberts*, Atlanta, Ga.—This paper is well worth while. Constrictive pericarditis is so relatively rare when compared to the frequency of congestive failure that the former condition may not be even considered. In the South, due probably to the few cases of rheumatic fever compared with colder climates, it is a rare condition, though in the last year I have seen three cases. The third, fourth, and fifth ribs were resected in one of these cases, according to Brauer's operation as modified by Graham and done by Elkin. In the advanced degree of dyspnea, ascites, and little cardiac reserve, the two-stage operation may be wise and safer. Another patient lived to be seventy-four years old, but autopsy revealed the constriction and multiple external adhesions but no calcification. Another patient at the age of thirty-four years had the usual signs of constriction, concretio cordis, dyspnea, and pedal edema for eight years, marked systolic retraction of the epigas-

trium, and the anterior left interspaces, but no Broadbent's sign posteriorly. Pick's disease is not only often missed when it is present, but also it may be suspected when it is absent.

As Dr. Sprague stated, Broadbent's sign is often absent. Its absence is no proof that constriction is not present. Its presence is confirming and intimates need for proof of constriction. Excellence in cardiac diagnosis would discover constriction before early heart failure develops, much less proceeds to the degree of extreme congestive failure. When the diaphragm is tied by adhesions to the liver and spleen, and the liver is large, expiration ceases to be normal, and after years of varying degree of dyspnea, extreme emphysema may develop in the young as in the thirty-four-year-old man mentioned above. Retraction of the posterior interspaces may occur without epigastric pulsation or retraction, or epigastric retraction without the posterior interspaces moving. A dull ache arising in the precordial region and felt through to the left scapular region is suggestive. The diaphragm may be flattened bilaterally both by the emphysematous lungs above or by the adhesions below, or by both conditions. The firmness and largeness of the liver are suggestive of constrictive pericarditis. The lower border of the liver may reach to the iliac spine. The costophrenic angles may be filled with dense adhesions and misinterpreted as the fluid of a bilateral hydrothorax due to congestive failure alone. The pulsus paradoxicus should indicate the right cardiac diagnosis. Every case of congestive failure of doubtful etiology should include the technic of inspiration with the fingers on the radial artery. The absence of the apex beat or its independence of position and gravity intimates that more than ordinary congestive failure is present. Previous rheumatic infection with too early signs of early failure or congestive failure should raise the question of constricting adhesions.

A careful fluoroscopic study by the cardiologist himself is well. The heart that seems to beat by standing still at once raises the question. The amplitude of the systolic contraction may be a mere flicker in constriction. The wall of the poor ventricle is drawn out, but it cannot pull in as it would. The dense streaks and shadows of a *concretio cordis* may be apparent in the fluoroscopic study and be missed in the teleogram. When calcification is suspected, films taken with the further aid of the Buckey apparatus, and laterally as well as anteroposteriorly, may bring out far more clearly the proof and the degree of the calcification.

This is a difficult differential diagnosis to make. One would do well to maintain a mental attitude of care not to overlook a constricting pericarditis rather than the more dogmatic attitude of satisfaction that it is certainly not present. Not every patient with constricting pericarditis has congestive failure at the time of examination, and by far the majority of cases of congestive failure have no constricting adhesions, but the differentiation involves care in examination and equal care in interpretation and conclusion. Dr. Sprague, as usual, has read a good paper and rendered another service.

*Dr. George Herrmann, Galveston, Texas.*—Dr. Sprague has brought to our attention a very important group of cases and has contributed observations that are of inestimable value. I think, however, that the enthusiasm for surgical intervention should not be allowed to pass unchallenged or without a word of caution. I have had just a few experiences that have impressed upon me the necessity for caution. First of all, it must be admitted that for the most of us the diagnosis of constrictive pericarditis is difficult to make with certainty. Our experimental studies suggested new diagnostic methods which may now be realized with the kymographic study of movements of the heart and the electrocardiographic survey of Barnes. No diagnostic stone must be left unturned, we must insist upon adequate evidence for I know of two instances in which the pericardium was explored and found to be smooth and free throughout. Such mistakes we should not make, of course.

The other, an error of omission, is even more difficult to avoid. I refer to the recognition of the possible presence of a scar of the preceding myocardial infarction in a patient with adhesive pericarditis stenocardia. It is often a question of the interpretation of the symptoms. I believe that we might state that if there is a history of an acute pericardial process having been preceded or accompanied by severe pain, one should be cautious in making a diagnosis of acute pericarditis. One case in point was a young man who told of having had four years previously an acute attack of precordial pain which was accompanied by a friction rub and diagnosed as acute pericarditis. He had never recovered his usual exercise tolerance and careful study revealed clinical, roentgenographic and cardiographic evidences of adhesive pericarditis. He was scheduled for operation, but three days before operation, while on his usual afternoon ride in the country, he collapsed and died. At autopsy he presented adhesive pericarditis, it is true; but the pericardium formed most of the anterior wall of the heart, so that the decortication in his case would not have been a very successful procedure.

Another patient gave me a story of an attack of pain eight years previously along with a friction rub and symptoms of a very distressing type, with cyanosis and collapse which were considered to be the result of pericarditis with effusion. The case was followed very carefully by a physician, and recovery seemed complete until eight years later when symptoms of heart failure appeared. The failure was more of the type that has been described so well by Dr. Sprague as failure of constrictive type. His congestive failure cleared up, and we were ready to have him operated upon. Fortunately for us he developed acute bronchopneumonia and died. He had adhesive pericarditis, it is true, on both sides of the heart, but anteriorly he had an aneurysm of the pericardium. There was a hole about 1.5 cm. in diameter through his left ventricular wall, and it was completely healed at the borders and the blood had been passing through it out into the pericardium and flowing back again. Operative procedure in this case would have been a difficult matter also.

I believe therefore that caution is in order in the diagnosis of constrictive pericarditis before undertaking surgical treatment. We cannot be too careful in the study of such patients.

*Dr. Harry A. Richter, Evanston, Ill.*—How much fluid is necessary in acute pericardial effusion to make a diagnosis? Williamson and Willy in 1918 showed that small effusions tend to localize in higher levels at the base of the heart rather than at the apex.

I recently cared for a man with coronary occlusion who had a paradoxical pulse and other signs of pericardial effusion, which gradually increased in severity over a period of seven months, when death occurred. At autopsy a thrombosis was present in the left anterior descending coronary artery, and areas of infarction in the anterior wall near the apex, and 300 c.c. of clear fluid was present in the pericardial sac. The question came up as to whether or not the patient could have been helped by paracentesis.

*Dr. A. R. Barnes, Rochester, Minn.*—Mr. Chairman, I am afraid that Dr. Sprague has oversimplified this question of diagnosis. I have no doubt that in his hands it is easy, but I haven't found it so in my own. He did not stress the electrocardiographic findings.

I was sorry that Dr. Herrmann did not take the opportunity to discuss them a little, because he and his associates have written a most excellent paper on the subject.

We are at present engaged in an investigation of the electrocardiographic changes in pericarditis. I would like to call your attention to two or three electrocardiographic changes that have been of assistance in making a diagnosis of pericarditis.

In the first place, the electrocardiogram may record and reflect the fact that coronary occlusion is complicated by pericarditis. I pointed that out in a little publication, and the characteristic feature is the upward rounding and slight elevation of the RS-T segment in all leads. That type of tracing occurring in the presence of known occlusion indicates unmistakably, as far as I know, that that patient has a complicating pericarditis.

Now after having made that observation, I have had the opportunity to observe acute inflammatory pericarditis, and I have some excellent examples in which acute inflammatory pericarditis was indicated by this peculiar upward rounding and elevation of all RS-T segments and in one of which it was impossible by any of our methods of clinical examination to make the diagnosis which was proved at autopsy.

A few years ago Dr. Whitten and I had an occasion to study this, and we were struck with the fact that in adherent pericarditis there were an unusual number of tracings in which the T-wave was negative in all three leads. Dr. Sprague called attention to the fact that the T-wave may be negative in Leads I and II, and I quite agree with that and that the S-T segment may have a contour which resembles more or less closely that observed in an old healed myocardial infarction. The occurrence of negative T-waves in all three leads is a rather unusual electrocardiographic finding in general and that alone, or especially if coupled with low voltage in all leads, calls for careful exclusion of pericarditis.

*Dr. Simon Dock, New York, N. Y.*—I would like to ask Dr. Sprague how many of his cases of restricted pericarditis or calcified pericardium were subjected to surgery and what the results were.

*Dr. James A. Lyon, Washington, D. C.*—I should like to ask Dr. Sprague what the surgical management of these cases has been.

*Dr. Sprague.*—I am sorry, Dr. Kerr, that I am not able to give you statistical data on the specific gravity of the fluids from the abdominal and pleural cavities. There were seven cases with pleural effusions, a transudate in each case.

Dr. Herrmann has wisely cautioned us about surgical attack on these cases. I agree with him entirely that the story of pain at the beginning of an attack showing later pericarditis should make us very suspicious about the underlying pathology. The point about Pick's disease, however, is that one very infrequently sees the onset of the condition. If he does see the early stages, it generally appears to be fairly easy to make the diagnosis of acute, then subacute, then chronic pericardial inflammation, progressing very slowly over a matter of months, associated with fever and the evidence of fluid in the pericardium. I should not feel that in most cases of coronary occlusion the patients we see would be threatened with surgery and resection of the pericardium because in coronary occlusion and certainly in those cases which develop aneurysm of the ventricle the heart is badly damaged and is always enlarged. In the cases of Pick's disease that we operate on, the heart is small.

The question of how much fluid is necessary for the diagnosis of acute pericarditis from a practical point of view is not very important, because in acute cases one does not do anything about the pericardial effusion unless the signs of cardiac embarrassment arrive, that is, fall in blood pressure, increasing distention of the veins of the neck and enlargement of the liver. If there is not enough pericardial fluid to produce the picture, it is not necessary to go after it with a needle except for your own diagnostic satisfaction. If the diagnosis of fluid in the pericardium is very questionable, it seems hardly worth while to try to tap the pericardium.

I agree with Dr. Barnes and Dr. Herrmann that it is very difficult to diagnose these cases of Pick's disease. In the past seven years we have had intensive interest in our clinic through Dr. White's group and Dr. Churchill's group. Before that we

had the unfortunate experience, when the Brauer operation of thoracotomy was being done, of going in and finding the heart entirely free from pericardial adhesion, both to the chest wall and between the layers of the pericardium.

I wish to agree decidedly with Dr. Barnes on the subject of the electrocardiogram. I mentioned only the findings which we had in all the cases, and we have come automatically to consider pericarditis when we see the S-T and T-wave change in all three leads which he has mentioned.

At the present time fifteen patients have been operated on. Seven have been completely cured; one was partially relieved; three died primarily of the disease itself; three died of complications. There are two patients living in whom the diagnosis is not proved. Unfortunately there is not time to discuss the details of the surgical treatment.

Discussion of the paper, "Studies on the Effect of the Action of Digitalis on the Circulation in the Presence of Congestive Heart Failure," by Drs. Stewart, Deitrick, and Crane.

*Dr. Drew Luten, St. Louis, Mo.*—Mr. Chairman: In his summary I understood Dr. Stewart to say that digitalis has no consistent effect on cardiac output. I should like to ask him whether this statement was meant to apply to the effect of the drug generally, including both the normal and the dilated failing heart, or whether it is applicable specifically to cases of congestive failure. I appreciate the fact that in the normal heart the effect is to decrease output, but I got the impression from his paper that in his cases of heart failure Dr. Stewart found a rather consistent tendency for output to be increased. I should like to ask him whether his findings agree with Harrison's, which were that in the cases of patients with dilated failing hearts digitalis produces no consistent effect on the systolic discharge.

*Dr. Stewart.*—I purposely made the statement that the cardiac output *may* increase because this being a relatively small number of cases, one can conceive of a situation in which, such as in the case of the one patient with auricular fibrillation to whom we gave digitalis, the total cardiac output per minute did not change appreciably. His heart rate slowed from 80 to 50, and the heart became smaller. Now the work chart of that patient showed that the work of his heart was to his advantage at the slower rate and with the smaller heart, although from the cardiac output one might not have suspected that.

I have had occasion, both before Dr. Harrison published his observations and later, to go over his findings and point out certain similarities between some of his observations and some of ours. Maybe those in which he observed no change in cardiac output or a decrease in cardiac output were those in which the heart was made too small a pump. There are no observations of his relating to cardiac size, so it is not profitable to discuss this point further.

There is dissimilarity between the observations reported by Harrison and the observations which we are reporting in the manner in which the observations were made. All of our observations were made immediately before digitalis was given and then within twenty-four hours afterward because we were of the opinion that the early effects of digitalis were perhaps the important ones. Those of Harrison were made at variable times, both before and after the drug was given.

Discussion of the paper, "Inhibiting Thyroid Activity in the Treatment of Cardiac Insufficiency, A Report of Four Cases," by Drs. Lyon and Horgan.

*Dr. William J. Kerr, San Francisco, Calif.*—It seems to me Dr. Lyon has shown the right spirit to come before us and present some of the later effects or end-results in the limited number of cases of patients treated by this method. I wish that



some of those who were so enthusiastic about total thyroidectomy a few years ago would likewise come before us and tell us something about their end-results.

On the shores of the Pacific we are now beginning to see some of the patients who were operated on in the first flush of enthusiasm, and the results in those we have seen are far from encouraging. I recently saw a literary writer who was able to carry on and do some productive work even with a bad heart, but since thyroidectomy it has been impossible for her to stay awake long enough to finish a sentence, which does not make her a very facile writer.

Our own series of cardiac cripples upon whom thyroidectomy was done is small. We had one patient, however, with a marked aortic stenosis and severe pain of anginal type, where there has been almost entire relief of pain following a total thyroidectomy. This patient is a draftsman for a manufacturing concern, and formerly he could not work very much on account of pain. He had complete relief from pain, which makes life tolerable, but now he cannot work very much because he goes to sleep all the time. We are not able to find the level where he is able to keep awake, is free from pain, and can do any work.

This subject is open for discussion. We have not personally had any experience with the method which Dr. Lyon and Dr. Horgan have been using, but there probably are a good many who can say something about the section of the sympathetic fibers in these cases.

*Dr. R. W. Langley, Los Angeles, Calif.*—Some of us in Southern California agree with Dr. Kerr with regard to the value to be placed upon thyroidectomy as a procedure in controlling congestive heart failure. I think this very interesting paper leaves us more in a quandary than ever as to the rationale of this or any procedure which has to do with the interference of thyroid gland function and its relation to control of heart disease.

I would like to ask Dr. Lyon about the operative time required for this procedure compared with the time required for thyroidectomy and also about the amount of shock which these patients show following the operation.

*Dr. Samuel Shelburne, Dallas, Texas.*—Mr. Chairman, I don't see how there can be any way to evaluate the work that Dr. Lyon has done because I doubt if any of us have been able to observe patients with this ingenious procedure. I think it deserves a trial. However, it would be preferable to leave the trial in his hands for a good while, until we see how the results of total thyroidectomy are going to come out.

I have under observation at the present time a patient on whom we did a total thyroidectomy in March, 1934. He is a typical case of chronic coronary heart disease and was thrown into an attack of coronary thrombosis by an injection of insulin in December, 1933. He had been a subject of diabetes for about five or six years prior to that time.

This is a case history on a lantern slide. It is unusually satisfactory. First of all, I want to call attention to the change in blood sugar and discuss that briefly. Soon after the operation, this patient, who had moderately severe diabetes with blood sugar running up to 300, was to all intents and purposes cured of the diabetes by the total thyroidectomy. (You will notice it took about six weeks to have an effect from the operation on various bodily functions, basal metabolism and blood sugar.) I think in the future, if we may judge by the few cases that have had total thyroidectomy, diabetes is going to be affected profoundly by this procedure. But, as Dr. Kerr queried, is it worth while to cure the diabetes when the patient has to endure the unhappy symptoms of myxedema? This patient, of course, developed symptoms and signs of myxoedema which were more disagreeable than those of diabetes. Several months after this operation, it became obvious to us we were either going to have a very, very unhappy patient or we were going to have to

put him on thyroid extract. You will observe that when enough thyroid was given to control the myxedema, the diabetes returned. I have been unable so far to find a happy medium.

Now, I have been interested for a good many years in the subject of edema, and I made some observations on edema in this patient. That is the point which I would like to pay most attention to at this time. The patient's edema was made worse by the operation. He developed one of the most extensive degrees of edema I have encountered in a fairly broad experience with these patients. It was so massive that I had to use needles to drain fluid from the subcutaneous tissue. Since Southey tubes were not available, we used Lindeman tubes which are just as good and, of course, cost much less. These were inserted under the skin of his legs, draining off large amounts of fluid. The edema was reduced. Thereafter we found that the usual diuretics were effective.

When the amount of thyroid, as shown in this chart by the depth of this black area here, was increased, this patient had less edema but he had a higher blood sugar and much sugar in the urine. It is obvious that this patient had less edema when he was on large doses (2 grains) of thyroid.

Dr. Blumgart, of Boston, advised me that a tenth of a grain or a fifth of a grain would be sufficient amount of thyroid to use. You see, in this instance, we cut down to about a fifth of a grain. During that period of low thyroid intake, his weight started right on up, and his edema returned. You see how frequently here we gave him mercupurin, a new diuretic which has proved very satisfactory to us. He does not have any sugar in his urine and his blood sugar is low. This will continue as long as we keep him on the low intakes of thyroid extract.

So, I would say that it is going to be a matter of time before we will be able to judge the effects of total thyroidectomy. This patient was one of the early cases, and he has been very closely observed. It seems to me that it is going to take a long time to find out whether we can strike a delicate balance between the various metabolic disturbances. There seems to be no question on the part of the men doing the work in Boston that this procedure is of great value in angina pectoris. This patient has had no pain since he had the operation. I sincerely doubt the value of the operation in the control of other symptoms and signs in heart disease or any great value in diabetes.

*Dr. M. H. Nathanson, Minneapolis, Minn.*—Dr. Kerr mentioned the physical and mental sluggishness and exhaustion of patients in whom a total thyroidectomy has been performed. I would like to suggest the use of a new substance, phenylisopropylamine (benzedrine), which appears to have a striking effect on these symptoms. Introduced recently by Prinzmetal and Bloomberg for the treatment of narcolepsy, I have found that there is a marked amelioration of such symptoms as fatigue, exhaustion, and drowsiness, which may be considered as mild narcoleptic manifestations.

I have not treated any patients following total thyroidectomy with benzedrine, but I have found striking improvement in the general condition of a group of patients with low metabolic rates who had little or no benefit from thyroid extract. The dose of benzedrine is small, 10 mg. once or twice a day. The peripheral sympathomimetic effects which might be very undesirable in cardiac patients, such as increase in cardiac output and the pressor action, are not produced by these small doses.

*Dr. Howard B. Sprague, Boston, Mass.*—I think perhaps I might be allowed to say one word since I come from the city where this procedure, complete thyroidectomy, originated. I merely wish to summarize the situation at present in Boston in this way by saying that at the Massachusetts General Hospital we have not performed any complete thyroidectomies for a considerable time, I think for a year; that at the other clinics in Boston, they are definitely in the stage of study-

ing the cases which have already been operated on and the enthusiasm for the procedure is definitely on the wane. Ever so often instances of quite remarkable relief after the procedure, whether related or not, are reported. The great difficulty is the one of selection of cases and no one that I know can tell before the operation what type of patient will be benefited. Dr. Lyon's procedure has the advantage of being a less serious operation and it appears that even after complete ablation of the gland the metabolism level does not correlate with the degree of clinical improvement. It may be that some other factor is involved, as Dr. Lyon's work suggests, and that his operation will give another series of cases which should be followed over a long period of time before the whole matter can be completely assessed.

*Dr. Merritt B. Whitten, Dallas, Texas.*—I would like to ask the essayist if any post-mortem study was made of the thyroid gland, in the cases that came to post-mortem examination, and if such a study was made, did it reveal any changes in the size or structure of the gland which might be considered a result of the operation?

*Dr. Lyon.*—The operation has been performed in 12 cases, 8 of angina pectoris and 4 of cardiac insufficiency. In the anginal group, 6 of the 8 patients have had no recurrence of angina pectoris for postoperative periods of from 5 to 28 months. One patient was not relieved of his attacks. There was one postoperative death.

Prior to operation the patients are kept at complete rest in bed for from two to eight weeks. In the cardiac insufficiency group, operation is not carried out until all signs and symptoms of congestive failure have disappeared. The patient is anesthetized by an inhalation of ethylene and a local infiltration of novocaine. A collar incision is used similar to that employed for a thyroidectomy. The operative time is about forty-five minutes.

We have made no biopsy or post-mortem study of thyroid tissue in this series of cases.

It is our opinion that metabolic readings are frequently not reliable indices of a patient's basal metabolism. This is especially true of patients who, because of aortic regurgitation, cardiac asthma, severe dyspnea, or extreme nervousness, are not able to cooperate in making the test. We, therefore, check the basal metabolic rate by the blood cholesterol level.

As to what constitutes improvement, we consider such changes in the patient's condition as the following:

1. A cessation, or a marked lessening in the frequency, of attacks of cardiac insufficiency.
2. A definite increase in the patient's ability to carry on regular employment without a return of symptoms of congestive failure.
3. A definite increase in the amount of exertion which the patient can undergo without discomfort, such as dyspnea, rapid heart action, or pain.
4. A lowering and stabilization of the patient's blood pressure or heart rate.

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## Original Communications

### A NEW METHOD FOR DETERMINING THE CIRCULATION TIME THROUGHOUT THE VASCULAR SYSTEM

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#### A PRELIMINARY REPORT\*

THE numerous contributions dealing with blood velocity or circulation time which have appeared in the literature during the past few years have greatly increased our knowledge concerning the rate of blood flow in man. Attention has been focused on this factor as it is related to the function of the heart and the thyroid gland, to polycythemia,<sup>1, 2</sup> to pituitary states<sup>3</sup> and to other pathological conditions. In addition, such generalized reactions as those produced by exercise<sup>4</sup> and artificial fever<sup>5, 6</sup> have been studied.

The methods previously described have not lent themselves to the determination of the circulation time to the various extremities. As a result, the use of this approach to the study of vascular impairment of the extremities has not, to our knowledge, been seriously considered. An ionization method recently described by McCracken, Sheard and Essex<sup>7</sup> may prove to be suitable for such studies, but it requires elaborate apparatus and is strictly a laboratory procedure. Calcium chloride<sup>8, 9</sup> has been used for the determination of circulation time from the elbow to the throat but was not widely used because of the danger of slough at the site of injection and the lack of satisfactory response in some patients. Careful observations of the reactions at the tips of the extremities were not emphasized, although all workers using calcium compounds intravenously are familiar with such reactions.

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The possibility of such a method was the incentive for the work herein reported.

It seems essential that the following conditions should be met in order to justify the use of any agent for intravenous circulation time studies.

1. The substance must be nontoxic in the dosage employed and, if possible, totally innocuous to the body or any of its parts.

2. The reaction evoked must be definite in both normal and pathological conditions.

3. The agent should be eliminated from the system with facility, so that repeated tests may be made within reasonable periods of time without jeopardizing the welfare of the patient.

4. The method should not influence the velocity of the circulation, at least until after the desired reaction has occurred.

5. The procedure should be technically simple.

6. It should permit the expression of normal and pathological states in terms of figures which will lend conciseness to the understanding of the conditions being studied.

The purpose of this paper is the presentation of an agent which, in our opinion, fulfills the above requirements, together with preliminary studies of its use in normal and pathological states.

*Preparation of the Agent.*—A solution containing 42 gm. of magnesium sulphate, 16 gm. of calcium gluconate, 0.9 gm. sodium chloride, and 1 mg. of copper sulphate in 100 c.c. of distilled water is prepared. This solution must be prepared carefully, as the calcium gluconate is in proportion, in a supersaturated solution. In order to obtain a state of supersaturation, the calcium gluconate must be fresh and free from any hygroscopic water. The calcium gluconate is added to the water in a partial vacuum with the water at the boiling point. When all of the calcium gluconate has entered into solution, the sodium chloride and copper sulphate are then added. Finally, the magnesium sulphate is added, and the solution is filtered through a double layer of filter paper which has been moistened with distilled water. The solution should, at this point, be crystal clear. It is placed in a sealed container and subjected for seventy-two hours to 12° C. temperature. At the end of this time, it is again filtered and measured, and any deficiency in volume is made up by the addition of distilled water. It is then autoclaved, according to the standard technic, and, after it has been removed from the autoclave, samples are taken to check on the hydrogen ion concentration.

In our experience with the use of hard glass containers, the pH of this solution tends to drop. It has been helpful to use a soft glass container to maintain a pH of 5.5 or higher, but if autoclaving reduces the pH below 5.5, it can be buffered with sodium phosphate or sodium

citrate. The only reactions we have observed following the use of this solution have occurred when it has been injected while at a pH of 3.5 or less.

*Toxicity.*—Meltzer and Lucas<sup>10</sup> in 1907 reported that magnesium salts, when injected hypodermically or intravenously, are highly toxic. They depress the heart muscle and the central and peripheral nervous systems. The daily requirements of magnesium are estimated at 0.6 gm. The ordinary diet contains 0.192 to 1.2 gm. (Sherman, Mettler and Sinclair,<sup>11</sup> 1910).

After absorption or with parenteral administration of small doses, the excretion of magnesium occurs practically exclusively through the kidneys, only a small part being excreted through the large intestine. Jacoby,<sup>12</sup> on the other hand, claims that, in the human subject, after parenteral injection of very large doses of magnesium against tetanus, the greater part is excreted by the intestines, although its concentration in the urine exceeds that of calcium.

The toxicity of the magnesium solution is probably an ionic action. It is thought that the ionic activity may be exerted only on the surface of the cell, especially by altering the permeability of the plasmic membrane and that the antitoxic actions also affect mainly the permeability.

The high resistance of cells to the penetration of ions makes any internal effects improbable. W. Straub<sup>13</sup> in 1912 demonstrated that calcium acts strictly upon the cell membranes. The promptness by which the effects can be removed by the addition of a second salt also speaks against absorption. It is very probable that the single salt solutions disturb the semipermeability of the membranes (J. Loeb, 1914<sup>14</sup>), thus interfering with the maintenance of the electric potential which determines irritability. Increased permeability would also produce chemical changes by permitting the entrance of foreign ions. The increase of either calcium or magnesium depressed the muscle and nervous structures. The effects of magnesium may, nevertheless, be removed by the addition of calcium. Calcium also antagonizes the inhibitory effects of potassium as well as the stimulant effects of sodium (Meltzer and Auer, 1908<sup>15</sup>). Even more complex relations were discovered by Joseph and Meltzer<sup>16</sup> in 1910. Injection of magnesium into the lymph sac produces a curare action, paralyzing the muscle nerve endings, but not the muscle. The excitability is restored by calcium. Perfusion of magnesium paralyzes the muscle as well as the endings. Calcium, by itself, then, has no restorative effect. Sodium restores only the muscle. Sodium plus calcium restores also the endings. Tadokoro<sup>17</sup> in 1918 asserted that the velocity of calcium ions through colloids is increased by the presence of magnesium salts, whereas the diffusion of magnesium ion is retarded by calcium salts. On the other hand, the diffusion of glucose through the cells is favored by calcium and retarded by magnesium.

The solution with which we are dealing is a true ionic solution; peculiar to ions, especially the ions with which we are dealing, is their antitoxic action. This antitoxic action must not be confused with the bacteriological meaning of the same expression. Loeb<sup>18</sup> and Meltzer and Auer<sup>19</sup> clearly showed that the toxicity of an electrolyte can be very greatly lessened by the addition of another suitable electrolyte, sometimes in a very small proportion. The mechanism of this antitoxic action has been explained at various times in various ways. Stewart,<sup>10</sup> in 1902, suggested that it might be explained in some cases by alteration of permeability preventing osmotic changes or the penetration of harmful ions. This work was confirmed by Loeb<sup>18, 20</sup> in his work on balanced salt ratios.

Mathews<sup>21</sup> attempted to show that the cations and anions are both concerned in the toxic and antitoxic actions and that the valency had no direct connection with either action. Although, however, the mechanism of this phenomenon is not clear, and no theory has ever fully explained it, it is known that calcium is especially and peculiarly antitoxic to magnesium.

The solution herein presented is not a balanced salt solution in the usual sense. It is balanced only in terms of its ionic toxicity. The calcium that this solution contains is present solely for its antitoxic action on the magnesium ions. Its principal purpose is not to reinforce the stimulus produced, although it may contribute in a minor way in this regard. Magnesium sulphate reacts to form a precipitate with most calcium salts and especially with those that are appreciably soluble. We have attempted to use calcium chloride, calcium sulphate, calcium levulinate, and calcium dextrinate, but have found calcium gluconate to be the most satisfactory. In our experience, this solution herein presented is nontoxic and does not give evidence of changing the heart rate, the blood pressure or the circulation time until after the limited and fleeting reaction we desire has passed. We have repeated this test frequently in the same individual without any deleterious effect.

The copper sulphate is used in this solution as a preservative against spores and molds. Molds are difficult contaminations to control, and, unless the solution is prepared and preserved immediately in ampules according to the technic for ampule preservation of the U.S.P. XI, spores are also common contaminating organisms. The present formula represents the eighty-seventh with which we have experimented, either chemically or biologically, and, hence, we term it Formula No. 87.

*Technic of Administration.*—The technic of administration is similar to that used for most intravenous circulation time tests. Two cubic centimeters of this solution is drawn up in a syringe that has been fitted with an 18 gauge intravenous needle. This solution is injected quickly and easily into the antecubital vein. The time is taken from the commence-

ment of the injection, because the response may come with a minimal amount of the drug, and because the time of injection is so short for such a small amount of solution (average:  $\frac{2}{5}$  to  $\frac{4}{5}$  sec.).

*Technic of Recording Results.*—Before the procedure has been started, the patient is informed that something is to be injected into the vein, that a definite sensation of heat will sweep over the body in less than a minute, and that he must observe carefully and not become confused. He is instructed to report immediately the site of sensation, as follows: “tongue,” “perineum” (we usually have him use the word “crotch,” because it is much shorter and less technical), “right hand,” “left hand,” “right foot,” “left foot.” If the order of sequence is changed, the patient, naturally, varies the order of report accordingly. The sensations may be present elsewhere in the body, but we have concentrated on the times to the above mentioned points. Stop watch times have been doubly checked in the series of tests we are reporting.

Usually, a mild spasm of the platysma and sternocleidomastoid can be observed immediately before the patient reports the sensation in the tongue. Occasionally, the confusion of the rapid action renders the first test unsatisfactory, but, once the patient has experienced the sensation, less difficulty is met with in the second attempt. We have repeated injections within ten minutes without any deleterious effect.

*Side Actions.*—In more than two hundred fifty injections with this material, we have had only one case of mild thrombosis of a vein. We have had no instances of sloughing. Early in our investigation, before the hydrogen ion concentration of the solution had been rechecked, after autoclaving, several subjects reported additional mild reactions from the use of this solution. These reactions took the form of chilly sensations recurring for periods up to eight hours. On checking the solution, however, we found that the hydrogen ion concentration was at 3.5 or less, and, since this has been rectified, we have had no such experience.

## RESULTS

The results presented below must be regarded as preliminary studies only. With the possible exception of the normal group, the figures are based on series too small to draw conclusions from. They are, however, interesting, and further work, to be published later, appears to confirm them generally. Table I contains all of the essential statistics. Certain points need clarification or emphasis. Six anatomical regions, namely, the tongue and throat, the perineum, the right and left hands and the right and left feet, were selected for this study. As may be seen, 40 tests were run (35 different subjects) on so-called “normal” individuals under forty-five years of age. The average figures, together with the range and the average deviations, are noted. We have used the term “blanks” to indicate tests in which no sensation was reported by



the patient in a given area. We have modified our solution since the beginning of this work, with the result that the number of "blanks" has been reduced. It is significant that, whereas, with the confusion of the first reaction, the patient may forget to report all areas, repetition in "normals" results in the reduction of the number of "blanks" to a

TABLE I  
CIRCULATION TIMES\*

	TONGUE THROAT	PERINEUM	RIGHT HAND	LEFT HAND	RIGHT FOOT	LEFT FOOT
<i>Normals</i>						
40 tests						
Average time	14.6	21.5	25.72	26.61	27.24	28.59
Range	7-22	12-32	11-43	17-43	10-46	13-48
Average dev.	$\pm 3.23$	$\pm 4.588$	$\pm 5.56$	$\pm 4.963$	$\pm 6.99$	$\pm 7.235$
Blanks†	0	6 tests	4 tests	9 tests	10 tests	12 tests
<i>Vascular Disease</i>						
Raynaud's syndrome spasm						
5 tests						
Average time	14.4	20.5	26.8	25.6	32.0	32.0
Range	12-17	12-27	21-31	21-29	29-34	29-34
Blanks	0	1 test	0	1 test	1 test	1 test
T. A. O.						
Organic						
9 tests						
Average time	15.22	29.33	29.42	29.0	34.5	34.75
Range	8-21	20-40	16-47	16-47	27-42	27-43
Blanks	0	2 tests	2 tests	2 tests	4 tests	4 tests
Arteriosclerosis						
Organic						
8 tests						
Average time	19.12	27.14	31.6	31.0	-	-
Range	14-28	20-36	20-44	20-44	28 & 44	28 & 59
Blanks	0	1 test	3 tests	3 tests	6 tests	6 tests
<i>Hyperthyroidism</i>						
5 tests						
A. Preoperative						
Average time	9.2	14.0	22.5	21.3	20.8	19.7
Range	8-11	11-17	16-30	16-30	15-26	15-26
Blanks	0	0	1 test	2 tests	0	1 test
B. Postoperative‡						
Average time	15.6	21.2	31.0	31.8	28.0	28.0
Range	14-17	19-24	26-36	26-36	23-31	23-32
Blanks	0	0	0	0	0	0

\*Time in seconds. Method of Spier, Wright, Saylor.

†No sensation in area.

‡One patient received x-ray therapy. The results were essentially the same as postoperative.

very small percentage. The persistently poor reactors may be patients with early vascular impairment, although we have accepted as "normals" only those in whom we could find no evidence of vascular damage. All tests were taken at rest. Whether the patient sat up or was lying supine did not seem to affect the figures, so long as the injected arm was at the heart level. It will be seen that the normal figures for arm-to-

tongue circulation coincide closely with those of other methods, although the range is somewhat wider. The figures to other areas are submitted as new and preliminary leads, but not as standards, because of the limited series reported at this time.

Study of the other figures, dealing with the small group suffering from the Raynaud's syndrome in which spasm is a marked factor, shows essentially no deviation from the normal, except that the figures for the times to the feet are increased. It is interesting that the one patient who gave no reactions in the perineum, left hand, and both feet had advanced, generalized sclerodermal changes. It was to be expected that these patients with spastic, but slight if any, organic change would show a fairly normal response when not in a spastic phase. We are at present trying to compare the reactions in the spastic phase as against those in the dilated phase.

In considering the organic diseases of the vascular tree (thrombo-angiitis obliterans and arteriosclerosis), we note definite increases in the average circulation times, as compared with the normals. In the thrombo-angiitis obliterans cases, the tongue and throat figure is increased, but this might well be within possible normal limits, considering the small series. It should be noted that the percentage of blank tests is increased and, in these cases, repetition of the test did not produce the sensation, as it frequently did in normals. An analysis of these cases showed that the figures were not dependent on the patency of the major vessels alone but that good collateral vessels would permit the passage of the substance rapidly. In general, the extremities with apparently the poorest circulation were the ones with the slowest times, or "blanks." In several instances, however, we were surprised by the reaction; this fact draws attention to the possibility that we may be dealing with a new method of value in studying the circulatory system as a whole. In one patient who had no reaction in the right foot, on repeated tests, we were able to get a definite though somewhat slow reaction after improvement following treatment.

The overlapping of the figures into the normal zone is readily explainable by the fact that, while thrombo-angiitis obliterans should be considered a generalized disease, it does not involve all areas equally and at the same time.

The figures obtained by the study of the arteriosclerotic group appear of especial interest. For this test, we selected only patients whose sclerosis was advanced, as determined by study in the Vascular Clinic. As will be noted, the averages are all markedly prolonged, but, in addition, the percentage of "blanks" shows a great increase. For example, in the right foot, in normals, the original figures were 10 blanks in 40 tests, or 25 per cent. In five instances repetition resulted in sensation. In the arteriosclerotic group, however, no sensation was felt in 6 out of

8 tests, or 80 per cent. and in no instance did repetition produce sensation. The increased time to the perineum in both thrombo-angiitis obliterans and sclerosis is of interest and worthy of further study.

The figures for hyperthyroidism are included merely to point out that the circulation time in this condition is decreased, when measured by this method, just as it is by other methods. Postoperatively, as may be noted, there is a definite prolongation of the circulation time.

#### DISCUSSION

No attempt has been made to survey completely the literature. This has recently been well done by Fishberg.<sup>22</sup> It should be stressed that, in most of the so-called circulation time tests, thus far devised, the "circulation time" is, in reality, circulation time plus reaction time. This is true of our test and may play an important part in the reaction times of arteriosclerotic patients. It also rendered tests of this type unsatisfactory for study of patients who are not mentally acute.

The ether circulation test of Iitizig<sup>23</sup> obviates the reaction time factor but will never be suitable for studies except from the cubital vein to the lung. The ionization method<sup>7</sup> is too complicated for widespread use, although it should give us the most accurate figures possible.

A death has been reported directly following a decholin test,<sup>3</sup> and also after the injection of saccharin followed by ether.<sup>24</sup> In addition, numerous severe reactions have occurred following each of these methods. Thus far, in more than two hundred fifty injections, we have had only the mild reactions noted above, when, following autoclaving, the pH of our solution dropped too low. Since correcting this factor, we have had no reactions except to the degree essential for the test.

The explanation of the "blanks" or lack of reaction in certain areas is not clear at present. Blood must reach them, or the tissues could no longer live. It is our feeling that "blanks" on the first test have slight significance, but, if persistent on repeated tests, it seems as though the blood travels so slowly that the solution is too dilute by the time it reaches the area to produce the sensation. Where the sensation is produced is also somewhat questionable. It is thought to be at the neuromuscular junction but perhaps occurs at the nerve endings of the skin.

In some instances, the sensations "repeat" throughout the body several times during the ten minutes after the injection. Why this occurs in certain individuals and not in others, when the same amount of solution is injected, is difficult to say at present.

We have been constantly improving our solution during the course of this study, although the fundamental constituents have remained the same. The formula herein presented is the most recent and the most satisfactory thus far produced, but it may not prove to be the ultimate. We are presenting our work in this preliminary form to stimulate

further studies along the lines of this somewhat different approach to the study of the circulation time to various points throughout the vascular system.

#### SUMMARY

1. The chemical formula and the method of preparation of a new solution for the study of the circulation time to various points throughout the vascular tree are presented. We have designated it Circulation Time Test Formula No. 87, or C.T.T. No. 87.

2. The technic of administration and of recording results is outlined.

3. Normal figures for the circulation time to the tongue and throat, perineum, right and left hands, and right and left feet are presented.

4. Figures on a small series of patients with the Raynaud's syndrome show no marked deviation from normal except that the time to the feet is prolonged.

5. Figures on a small series of patients with thrombo-angiitis obliterans show a tendency to a more prolonged circulation time than that of normals.

6. Figures on a small series of patients with arteriosclerosis show a tendency to a more prolonged circulation time than that of normals.

7. Figures on a series of patients with hyperthyroidism showed a definite decrease in the circulation time, with this method as with others previously reported. The circulation time is prolonged after thyroidectomy.

8. This paper represents a preliminary study and will be followed by a more detailed paper, covering work now in progress.

#### REFERENCES

1. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease; The Velocity of the Blood Flow and Its Relationship to Other Measurements of the Circulation, *Medicine* 10: 1, 1931.
2. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *AM. HEART J.* 8: 766, 1933.
3. Macy, J. W., Claiborne, T. S., and Hurxthal, L. M.: The Circulation Rate in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), *J. Clin. Investigation* 15: 37, 1936.
4. Ellis, L. B.: Circulatory Adjustments of Moderate Exercise in Normal Individuals With Particular Reference to Interrelation Between Velocity and Volume of Blood Flow, *Am. J. Physiol.* 101: 494, 1932.
5. Kopp, I.: The Velocity of the Blood Flow in Therapeutic Hyperpyrexia, *AM. HEART J.* 11: 475, 1936.
6. Kissin, M., and Bierman, W.: Influence of Hyperpyrexia on Velocity of Blood Flow, *Proc. Soc. Exper. Biol. & Med.* 30: 527, 1933.
7. McCracken, E. C., Sheard, C., and Essex, H. E.: (a) The Effects of Physico-physiologic Agents and of Drugs on the Circulation Time of the Blood of Dogs as Measured by Ionization Methods, *Proc. Staff Meet., Mayo Clin.* 10: 600, 1935. (b) The Circulation Time of the Blood of Dogs, Before and During the Digestion of Food, Determined by the Ionization Methods, *Proc. Staff Meet., Mayo Clin.* 10: 548, 1935.
8. Hirschsohn, J., and Maendl, H.: Notiz zur Kenntnis der Hämodynamik beim Pneumothorax, *Beitr. z. Klin. d. Tuberk.* 49: 64, 1921-1922.

9. Keller, H.: Ueber Veränderung der Blutumschlagszeit, *Wien. Arch. f. inn. Med.* 12: 1, 1909.
10. Meltzer, S. J., and Lucas, D. R.: Physiological and Pharmacological Studies of Magnesium Salts: V. The Influence of Nephrectomy Upon Their Toxicity, *J. Exper. Med.* 9: 298, 1907.
11. Sherman, H. C., Mettler, A. J., and Sinclair, J. E.: Calcium, Magnesium and Phosphorus in Food and Nutrition, U. S. Dept. of Agriculture Exper. Stations Bull. No. 227, 1910.
12. Jacoby, N.: Ueber die Ausscheidung von Magnesium durch den Harn, *Biochem. Ztschr.* 74: 131, 1916.
13. Straub, W.: Die Bedeutung Zellmembran, *Verhandl. d. deutsch. Gesellsch. Naturforscher u. Aerzte* 84: 192, 1912.
14. Loeb, J.: Is the Antagonistic Action of Salts Due to Oppositely Charged Ions? *J. Biol. Chem.* 19: 431, 1914.
15. Meltzer, S. J., and Auer, J.: The Antagonistic Action of Calcium Upon the Inhibitory Effect of Magnesium, *Am. J. Physiol.* 21: 400, 1908.
16. Joseph, D. R., and Meltzer, S. J.: A Demonstration of the Inhibitory Effect of Magnesium Upon Normal and Artificial Peristalsis of the Stomach and Duodenum, *Proc. Soc. Exper. Biol. & Med.* 7: 95, 1909-1910.
17. Tadokoro, T.: Mutual Action of Calcium and Magnesium Salts on Their Diffusion Through Colloids and the Physiological Meaning of These Salts, *J. Tokyo Chem. Soc.* 39: 423, 1918.
18. Loeb, J.: Ionization of Proteins and Antagonistic Salt Action, *J. Biol. Chem.* 33: 381, 1918.
19. Stewart, G. N.: A Contribution to Our Knowledge of the Action of Saponin on the Blood Corpuscles, *J. Exper. Med.* 6: 257, 1902.
20. Loeb, J.: Die Entgiftung von Kaliumsalzen durch Natriumsalze, *Biochem. Ztschr.* 31: 450, 1911.
21. Matthews, A. P.: The Toxic and Anti-toxic Action of Salts, *Am. J. Physiol.* 12: 419, 1904-1905.
22. Fickler, A.: Chapter on Circulation Time (in a monograph shortly to be published).
23. Hittag, W. M.: Measurement of Circulation Time from Antecubital Veins to the Pulmonary Capillaries, *Proc. Soc. Exper. Biol. & Med.* 31: 935, 1934.
24. Leinoff, H. D.: Complications Following Use of Saccharin and Ether as a Circulation Time Test, *J. A. M. A.* 105: 1759, 1935.

# THROMBOANGIITIS OBLITERANS OF THE CORONARY ARTERIES AND ITS RELATION TO ARTERIOSCLEROSIS\*

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**T**HROMBOANGIITIS obliterans (Buerger's disease) is recognized clinically and anatomically as a characteristic entity, particularly in its early stages. Besides the vessels of the extremities, this disease occasionally involves the abdominal branches of the aorta and the vessels at the base of the brain. To judge from the relevant literature, patients afflicted with this disease of the peripheral vessels sometimes reveal cardiac symptoms and, though rarely, may die unexpectedly from myocardial failure. Autopsy reports of such instances are rare. Almost invariably the gross and microscopic examination of the coronary arteries reveals arteriosclerosis with narrowing or closure of the lumen of the coronary arteries or a coronary thrombus. The myocardium often shows fibrosis or an infarct. Only very rarely are instances encountered in the literature in which the coronary lesions were interpreted as thromboangiitis obliterans. A critical analysis of these rare cases, however, does not corroborate the diagnosis, either because the description of the relevant lesions was not clear enough and no illustrations were included or because the lesions of the coronary arteries, although sclerotic in type, were interpreted as having been the result of a previous thromboangiitis obliterans. The reason for this interpretation is that either the patient revealed the classical picture of thromboangiitis obliterans of the peripheral vessels or did not belong to the age group in which coronary arteriosclerosis "normally" occurs.

The purpose of this communication is to relate an instance of outspoken thromboangiitis obliterans of the coronary vessels in which the process in places was so recent that the histological picture was characteristic. In other portions the vessel disease was apparently much older and the vessel changes could easily be confused with those of arteriosclerosis. A review is also given of those cases of thromboangiitis obliterans with autopsy reports in which changes in the coronary arteries were encountered. The relation of such changes, usually arteriosclerotic in nature, to thromboangiitis obliterans is also discussed.

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Dürck<sup>8</sup> in 1931 reported a number of instances of sudden death among which was that of a thirty-nine-year-old male with thromboangiitis obliterans of the lower extremities. There was also severe narrowing of the coronary arteries in this instance.

Brofeldt<sup>4</sup> in 1932 published a monograph on "necrosis of the extremities." He described a sixty-five-year-old male who had the clinical symptoms of Buerger's disease. Autopsy revealed a dilatation and degeneration of the heart with generalized arteriosclerosis and thromboangiitis obliterans of the abdominal aorta. In a fifty-six-year-old male sclerosis of the coronary vessels was found.

Jäger<sup>11</sup> in 1932 described three instances. In the first (a forty-eight-year-old male) the right coronary artery was almost, and the descending branch of the left coronary artery completely, occluded by "grayish tissue." Histologically the coronary arteries revealed areas of intimal thickening and fibrosis with a number of small sized blood vessels and eccentrically displaced small lumina. Between the internal elastic lamella and the organization tissue within the lumen there was a deposition of hyalin which in a few regions contained a network of elastic lamellae. Occasionally some calcification was present. In the second instance (a thirty-nine-year-old male) arteriosclerotic thickenings were found in the coronary arteries. In the third instance (a fifty-two-year-old male) an occlusion by a thickened intima of the descending branch of the right coronary artery was found.

Ehrström<sup>9</sup> in 1933 reported three instances of thromboangiitis obliterans with changes in the coronary arteries. In a twenty-four-year-old male the left coronary artery was obstructed by a thrombus. In a twenty-one-year-old male autopsy revealed a large myocardial infarct and obliteration of the coronary arteries in places. In a forty-seven-year-old male the left coronary artery contained an organized and canalized thrombus. The author stated that in Cases 1 and 3 it appeared quite certain that the coronary arteries had been the seat of a disease similar to that seen in the peripheral vessels in thromboangiitis obliterans.

De Blasi<sup>3</sup> in 1934 described in a thirty-one-year-old male a marked narrowing of the left coronary artery at a distance of 2 cm. from its mouth. Histologically this artery showed a subintimal cushion which occupied three-quarters of the lumen of the vessel. The endothelial lining appeared normal. The internal elastic lamella was delicate, but there was an interruption of its continuity in the region of the subintimal proliferation.

Birnbaum, Prinzmetal, and Connor<sup>2</sup> in 1934 described an instance of generalized thromboangiitis obliterans in a nineteen-year-old male. They mentioned that branches of the coronary arteries showed intimal thickening. Neither the aorta nor its major branches were involved.





TABLE I—CONT'D

14	Ehrström	24	Male	Thrombus	Left coronary artery	Infarct Degenerative changes	“Quite certain that the coronary ar- teries had been the seat of a dis- ease similar to that seen in the peripheral vessels in thrombo- angiitis obliterans”
15		21	Male	Obliteration	Both coronary arteries		
16		47	Male	Thrombus	Left coronary artery		
17	de Blasi	31	Male	Narrowing	Left coronary artery	Fibrosis	
18		19	Male	Intimal thickening	Both coronary arteries	Degenerative changes	
19	Averbuck and Silbert	43	Male	Thrombosis	Both coronary arteries	Infarct	
20		60	Male	Mild arteriosclerosis	Both coronary arteries		
21		42	Male	Sclerosis	Both coronary arteries		
22		42	Male	Arteriosclerosis	Both coronary arteries		
23		56	Male	Severe arteriosclerosis	Both coronary arteries	Infarcts Infarcts	
24		44	Male	Mild arteriosclerosis	Both coronary arteries		
25		42	Male	Thrombosis	Right coronary artery		
26		53	Male	Occlusions	Left circumflex and an- terior descending branch		
27		48	Male	Recent and old throm- bus	Anterior descending branch	Infarcts	
28		56	Male	Occlusions	Left anterior descending and branch of right coronary artery		
29	van Dooren	38	Male	Occlusion	Descending branch of right coronary artery	Infarct	“Because of the inflammation sur- rounding the nerve trunks, the changes in the arteries were thought to be characteristic of thromboangiitis obliterans”
				Intimal thickening Obliteration	Both coronary arteries Arterioles		
30	Telford and Stopford	26	Male	Reduction in caliber	Both coronary arteries	“Heart muscle heavily in- filtrated with blood”	The statement was made that the re- duction in caliber was due to thromboangiitis obliterans.

Averbuck and Silbert<sup>1</sup> in 1934 reported the autopsy findings in sixteen cases of thromboangiitis obliterans. In ten instances coronary lesions were described. Coronary thrombosis was found three times. The youngest patients were forty-two years old (three). In none of these 16 cases was thromboangiitis obliterans of the coronary vessels described.

Van Dooren<sup>7</sup> in 1934 reported Buerger's disease involving the lower extremities in a male thirty-eight years old. Autopsy revealed a recent infarct of the heart. The walls of the right and left coronary arteries were thickened. The descending branch of the left coronary artery was cordlike without a recognizable lumen. The microscopic examination of the coronary arteries revealed an obliteration of many of the arterioles. In other portions the lumina were narrow, irregular and eccentrically placed. The thickened intima showed no signs of organization. The internal elastic membrane was very thin or absent. The nerve trunks in some of the sections were surrounded by numerous polymorphonuclear leucocytes. The author remarked that the changes in the arteries resembled those seen in arteriosclerosis and that there was no evidence of inflammation of the arteries. However, the inflammation surrounding the nerve trunks, in the author's opinion, was characteristic of thromboangiitis obliterans.

Telford and Stopford<sup>17</sup> in 1935 described thromboangiitis obliterans in a twenty-six-year-old male (Case 2). They mentioned that the coronary arteries were much reduced in caliber by thromboangiitis obliterans. A description of these changes, however, was not given.

The literature reviewed shows that coronary lesions were found in 30 cases of thromboangiitis obliterans in which an autopsy was performed. An analysis of these cases reveals that in a vast majority the lesions of the coronary arteries were arteriosclerotic, with or without coronary thrombosis. Perla<sup>14</sup> and Telford and Stopford<sup>17</sup> mentioned an instance of thromboangiitis obliterans of the coronary arteries. In both, however, the descriptions of the lesions of the coronary arteries or illustrations of such lesions were lacking. Neither Ehrström<sup>9</sup> nor van Dooren<sup>7</sup> described changes characteristic of thromboangiitis obliterans in the coronary arteries, though these authors referred to the occurrence of this disease and believed their cases to be characteristic.

Table I is included to summarize the changes in the coronary arteries and in the myocardium in those instances of thromboangiitis obliterans which, coming to autopsy, showed coronary lesions. The table also gives the names of the authors, and the age and sex of the patients.

The changes in the coronary vessels and the myocardium are apparent. It is interesting to note that all patients were males.

In the following report an outline is given of the clinical history and the pertinent autopsy findings of an instance of thromboangiitis obliterans involving the vessels of the lower extremities and the coronary vessels. The changes in the latter were pathognomonic.

## REPORT OF CASE

*Clinical Note.*—A thirty-five-year-old male who was known to have had the characteristic symptoms of intermittent claudication over a period of about six years developed an upper respiratory infection from which he quickly recovered. As he was about to leave the house some time after his recovery, he suddenly collapsed and died instantaneously. At the time of the autopsy, no history could be obtained of previous ailments referable to the heart. As far as could be learned from various physicians, who at one time or another had attended the patient, the arterial blood pressure had always been normal, and there were no other abnormal findings.

*Autopsy Findings.*—The autopsy was confined to the lungs, heart and vessels of the lower extremities. The heart weighed about 350 gm. The valvular apparatus was intact. There were no mural thrombi. The myocardium was reddish gray and showed a number of small and large light gray dots and streaks and a few gray plaques, not exceeding 0.3 by 0.6 cm. in longest dimensions. These were largely in the anterior wall of the left ventricle but were also present in the wall of the right ventricle.



Fig. 1.—Thromboangiitis obliterans of a coronary vein. Note the resemblance to granulomatous lesions, such as tuberculosis (hematoxylin eosin preparation  $\times 95$ ).

The heart was dilated. The coronary arteries were markedly sclerosed and thickened by many hyalinized and calcified plaques which constricted their lumina. In various places there were also a number of atheromatous cavities and ulcers within the coronary arteries. The descending branch of the left coronary artery at a distance of about 2.5 cm. from its mouth was almost completely occluded by an intimal thickening which at one portion was covered by a reddish thrombus. The anterior and posterior tibial arteries also showed gross evidence of severe arteriosclerosis, their lumens being occluded at various places by old thrombi.

The nature of the disease of the coronary arteries was disclosed by the histological examination.

*Histologic Examination.*—Sections which were taken through the larger branches of the coronary arteries at points of narrowing showed various types of lesions. Some of the arteries revealed a marked intimal proliferation with much hyalinization and fibrosis. Other arteries showed just beneath the fibrosed intima atheromatous cavities containing many large histiocytic cells, the cytoplasm of which was filled with minute fat globules. There were also present typical cholesterol slits in a

network of a necrotic material. The media showed no changes of note, and the adventitia was slightly thickened. When serial sections were cut from the regions of the atheromatous cavities, a few fields were encountered showing infiltration of polymorphonuclear leucocytes with a few lymphocytes and occasional giant cells, the nuclei of which were distributed throughout the cytoplasm. These foci were found



Fig. 2.—Thromboangitis obliterans of a branch of a coronary artery. Note the rich granulation tissue forming the thrombus and the periarteritis (van Gieson preparation,  $\times 95$ ).

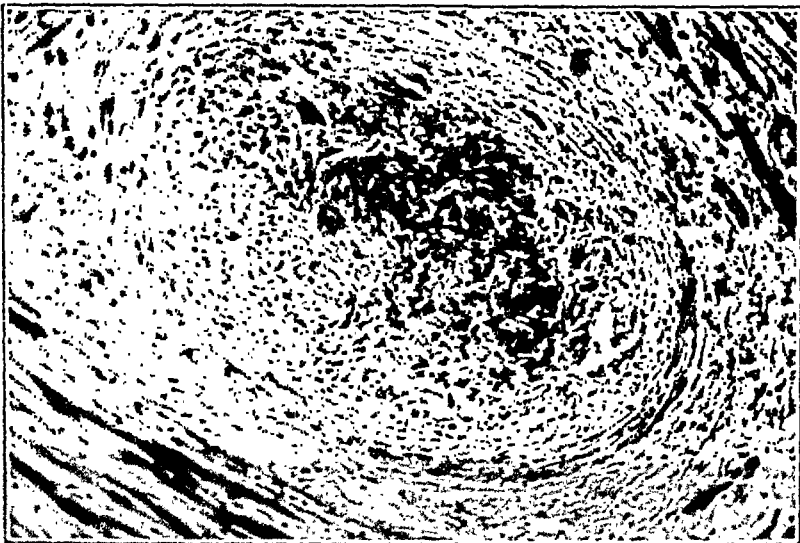


Fig. 3.—Thromboangitis obliterans of a branch of a coronary artery. Note the giant cells within the thrombus (van Gieson preparation,  $\times 95$ ).

within and covering the intima adjacent to the atheromatous cavities but were also seen covering atheromatous ulcers. Other sections of the coronary arteries showed a more or less circumscribed intimal fibrosis with only a few cellular elements. Capping these lesions were a number of polymorphonuclear leucocytes and several giant cells. The giant cells were surrounded by histiocytic cells and a number of polymorphonuclear leucocytes. Much fibrin was also seen adjacent to the giant cell foci.

The adventitia in this region was considerably fibrosed and infiltrated by a few lymphocytes. Sections which were taken from the smaller coronary vessels also revealed severe changes. On superficial examination some of the vessels could not be recognized as such without the aid of an elastic stain. At the first glance the lesions in question appeared to be granulomatous in nature, surrounded by fibrous capsules. The fibrous capsules, however, proved to contain some elastic fibers, and further sections revealed that what had appeared to be a granuloma was a thrombus, completely occluding the blood vessel. Both arteries and veins were involved. The thrombus consisted of a number of polymorphonuclear leucocytes, lymphocytes, a few endothelial cells and several giant cells, many of which were surrounded by fibrin and polymorphonuclear leucocytes. Many young connective tissue cells extended from the walls of the vessels into the lumina. Some of the sections showed a new formation of blood capillaries extending into the thrombus. Often the thrombotic material occluded the vessels, while in other vessels only a minute slitlike opening forming a channel for the passage of blood could be made out. The intima of these vessels was only slightly thickened. The media showed an infiltration of lympho-



Fig. 4.—Arteriosclerosis with atheromatous cavity (hematoxylin eosin preparation,  $\times 50$ ).

cytes and polymorphonuclear leucocytes. Also the adventitia was infiltrated with a similar type of cell and showed varying degrees of fibrosis. In other sections the giant cells predominated. Because of the fact that the entire wall of the vessel in some of the sections was infiltrated by inflammatory cells it was difficult, at first, to recognize the lesion in question as a thrombosed vessel. On section some of the smaller vessels showed minute emboli consisting of cells similar to those which were found in the proximal part of the vessels. The walls of these smaller vessels appeared normal.

Sections of myocardium showed large areas of fibrosis separating the muscle fibers from one another. In some of the sections only minute islets of muscle fibers were found completely surrounded by dense connective tissue. The latter was poor in nuclei. In other fields newly formed connective tissue with fibroblastic cells and endothelial cells was seen, the cytoplasm of these cells containing small pigment granules. These areas could easily be interpreted as small infarcts.

Because of the fact that some of the lesions encountered were obviously very early, it was thought that an extensive search for microorganisms might reveal the causative agents. A number of sections were stained according to the Gram-Weigert and

Giemsa methods, and various silver stains were used for the demonstration of spirochetes. None of these sections, however, revealed microorganisms.

The peripheral blood vessels showed the characteristic picture of arteriosclerosis in some instances, and in others of thromboangiitis obliterans with many organized



Fig. 5.—Note the thrombus with giant cells and the atheromatous cavity in the lower right of the picture (iron hematoxylin eosin preparation,  $\times 50$ ).

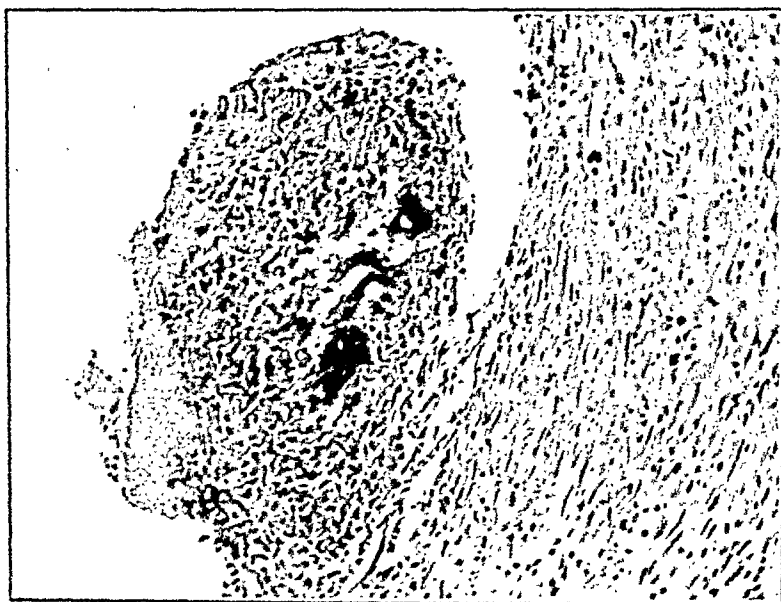


Fig. 6.—Same as Fig. 5. Higher magnification. Note the giant cells in the thrombus (iron hematoxylin eosin preparation,  $\times 150$ ).

and organizing thrombi. Some of the latter contained polymorphonuclear leucocytes, fibrin, and a number of miliary giant cell foci. The perivascular spaces revealed much connective tissue uniting arteries and veins.

**Surgery.**—A thirty-five year old male, who for the preceding six years had occasional symptoms of Buerger's disease confined to the lower extremities, died sud-

denly following a "grip infection." The autopsy revealed severe thromboangiitis obliterans of the coronary vessels and vessels of the lower extremities, in addition to arteriosclerosis. The myocardium showed a diffuse fibrosis with multiple old and organizing infarcts.

#### DISCUSSION

This case is interesting in several respects. The abruptness of the death without apparent premonitory symptoms is remarkable. Equally remarkable is the fact that the patient survived as long as he did in view of the very severe changes in the coronary vessels and myocardium. The lesions in the coronary vessels were characteristic of thromboangiitis obliterans.

After the histological findings were evaluated, a further investigation of the clinical history revealed a few additional facts which, retrospectively, in view of the anatomical findings, seemed significant. The paternal grandfather of the patient and his father's brother died of coronary thrombosis. The patient's father suffered from attacks of angina pectoris. In response to repeated questioning after the autopsy, the relatives denied that the patient had ever had attacks of substernal pain or dyspnea, but the following facts were brought out: Whenever the patient was confronted with minor physical strain, he had attacks of profuse sweating. It was recalled that on occasions when the patient had to raise his arms to hang a picture, this exertion was accompanied by sweating and such severe fatigue that he was forced to rest. None of these attacks were accompanied by dyspnea or pains of any type. In the light of the autopsy findings, it seems probable that these slight attacks of perspiration and weakness of the arms can be linked with the coronary disease and the myocardial changes and may possibly be interpreted as "abortive angina pectoris." As far as the anatomical findings in angina pectoris are concerned, it was concluded from a previous study (Saphir and coworkers<sup>16</sup>) that angina pectoris may be linked with a labile myocardium which may fail suddenly. To the morphologist, as a rule, coronary sclerosis and myocardial fibrosis, or as in this instance, thromboangiitis obliterans of the coronary arteries with resulting myocardial changes are the anatomical entities by means of which a diagnosis of labile myocardium may be made. In other words, the severe myocardial changes found in this heart could easily have been the cause of anginal or anginoid attacks of which the patient was scarcely conscious. The severity and extensiveness of the myocardial changes resulting from the thromboangiitis obliterans of the coronary vessels may in part also be explained by the relative youth of the patient and undeveloped collateral circulation of the coronary arteries. The final cause of death was a small thrombus in the descending branch of the left coronary artery.

As was stated above, cases of thromboangiitis obliterans of the coronary arteries are very rare. With the exception of two instances re-



ported by Perla<sup>14</sup> and by Telford and Stopford,<sup>17</sup> who mentioned thromboangiitis of the coronary arteries but who neither described nor illustrated such lesions, they have, as far as I have been able to find, not been described. Because of the fact that some of the lesions in this instance were acute and therefore, according to Buerger,<sup>5</sup> specific, this diagnosis could easily be made on microscopic examination. The acute inflammation of the adventitia, media, and intima, the miliary lesions consisting of polymorphonuclear leucocytes, histiocytic cells and giant cells, the lesions which at first glance may easily be confused with miliary tubercles or gummas, which, however, were shown to be within the blood vessels, constituting a thrombus, were unmistakable.

In addition to these lesions, however, other changes were encountered which were interpreted as arteriosclerotic in nature. Plain intimal thickenings with reduplication of the internal elastic layer and the formation of atheromatous cavities were significant in this respect. Occasionally, however, apparent transitions from thromboangiitis obliterans to arteriosclerosis were observed, thus rendering it difficult to differentiate between a thrombus arising on an atheromatous basis and a later stage of thromboangiitis obliterans, when organization of the thrombus has taken place. Occasionally the presence of a few giant cells in the latter revealed the true nature of the disease. The question arises as to whether the arteriosclerosis of the coronary arteries is a coincidental occurrence in no way related to thromboangiitis obliterans, whether the coronary sclerosis is merely a different stage (end stage) of thromboangiitis obliterans, or whether the coronary sclerosis developed as an entirely different entity on the basis of thromboangiitis obliterans.

Lemann<sup>12</sup> has raised the question as to whether or not it is a coincidence that coronary occlusion should be found in four out of five autopsies on victims of thromboangiitis obliterans. Buerger<sup>5</sup> stated that thromboangiitis obliterans and arteriosclerosis may be associated. Though not likely a concurrence without cause and effect relation, the simultaneous occurrence of these two diseases of the coronary arteries in older patients can never be ruled out as coincidence.

It is obvious that in early and late stages characteristic differences exist between thromboangiitis obliterans and arteriosclerosis. The region of the organized thrombus in the former disease is almost completely devoid of elastic tissue, whereas elastic lamellae are found in arteriosclerosis (Buerger<sup>5</sup>). The reduplication of the internal elastic lamella is also characteristic of the latter disease. However, Buerger<sup>5</sup> mentioned that where the lesion of thromboangiitis obliterans is of long duration (years) secondary thickening of the intima takes place with corresponding proliferation of the elastic fibers that can be confused with arteriosclerosis. Jäger<sup>11</sup> also maintained that in late stages a differentiation between these two diseases is hardly possible. In this instance a number of arteries showed occluding or partially occluding lesions which con-

sisted of old connective tissue with or without hyalinization; there was no new formation of elastic fibers. Here and there an occasional phagocytic cell with pigment granules in its cytoplasm was encountered. Other vessels revealed more circumscribed intimal thickenings with hyalinization, which thickenings were identical histologically with early arteriosclerotic lesions. However, when more sections were studied, minute vessels or blood pigment granules were occasionally encountered in the seemingly hyalinized region. These changes, which were found particularly in the smaller branches of the coronary arteries easily, may be interpreted as end stages of thromboangiitis obliterans. Some of the large branches of the coronary arteries, however, revealed obvious atheromatous cavities at the border between the intima and media with fat-containing cells and cholesterol slits. Some of these atheromatous cavities had perforated, thus producing atheromatous ulcers. The intima close to the atheromatous cavities and, in some instances, the recent thrombus covering the atheromatous ulcers revealed miliary lesions with polymorphonuclear leucocytes and giant cells, typical of thromboangiitis obliterans. In other words, the characteristics of arteriosclerosis and thromboangiitis obliterans were found in a single lesion. The age of the patient and the fact that in other vessels thromboangiitis obliterans predominated suggest the possibility that the thromboangiitis obliterans produced the initial changes which resulted in arteriosclerosis and atheromatosis. It seems quite clear that in older instances, changes which in their earlier stages were specific for thromboangiitis obliterans became less and less characteristic, and only fibrosis and hyalinization remained. These lesions, however, apparently formed the basis of the arteriosclerosis. Occasionally the causative agent of thromboangiitis obliterans apparently persisted, thus explaining the giant cell foci in the region of the atheromatous ulcer. It is, therefore, quite possible that true arteriosclerosis developed secondarily on the primarily diseased vessel. In a previous study<sup>15</sup> it was shown that arteriosclerotic lesions developed secondarily on a primary syphilitic arteritis. Karsner<sup>12</sup> stated, "It is conceivable that the changes (periarteritis in the coronaries of young rheumatic fever patients) might subsequently become transformed to those of coronary sclerosis." From this it would seem quite possible that the severe arteriosclerosis developed secondarily on the basis of the primary thromboangiitis obliterans. Arteriosclerosis is also often found in peripheral arteries which are the seat of thromboangiitis obliterans. It is also quite significant in this respect that there are reported in the literature a number of instances of thromboangiitis obliterans of the peripheral vessels, occurring in relatively young individuals with severe coronary arteriosclerosis. Naturally, many of these reports are purely clinical. The review of the literature, however, reveals that coronary arteriosclerosis was found at autopsy in 12 out of 30 hearts of patients who died before the age of forty years; one of these

died at the age of nineteen years; five between twenty and thirty years, and six between thirty and forty years. The high incidence of coronary arteriosclerosis in this age group is significant and points to a distinct relationship between thromboangiitis obliterans and coronary arteriosclerosis and probably arteriosclerosis in general. The fact that syphilitic and rheumatic lesions and also thromboangiitis obliterans can be the primary lesions underlying a later developing arteriosclerosis is additional evidence for primary inflammation as at least one etiological factor in arteriosclerosis.

#### SUMMARY

The literature dealing with changes in the coronary arteries as shown by post-mortem examinations of instances of Buerger's disease is reviewed, and thirty such cases are recorded. The lesions in the coronary arteries vary from simple intimal thickenings to severe arteriosclerosis and coronary thrombosis. In four instances the belief was expressed that the coronary lesions were characteristic of thromboangiitis obliterans. In none of these, however, was there given a clear-cut description of the coronary lesions or illustrations showing the characteristic lesions. An instance of sudden death is reported. The patient had shown clinical evidence of Buerger's disease but no evidence of cardiac lesions. The autopsy revealed severe thromboangiitis obliterans of the coronary vessels, coronary arteriosclerosis, multiple small infarcts and fibrosis of the myocardium. Sections of the coronary arteries showed, in addition to uncomplicated lesions of thromboangiitis obliterans, a combination of thromboangiitis obliterans and arteriosclerosis. Because of these findings and because of the fact that, according to the pertinent literature, coronary arteriosclerosis was found rather frequently in relatively young patients afflicted with Buerger's disease as proved by autopsy, the question of the relation between these two diseases is discussed, and the possibility is considered that a primary inflammatory lesion of the artery may be at least one factor in the causation of arteriosclerosis. Syphilitic arteritis, rheumatic arteritis, and also thromboangiitis obliterans may each constitute the primary inflammatory factor.

#### REFERENCES

1. Averbuch, S. H., and Silbert, S.: Thrombo-angiitis Obliterans: IX. Cause of Death, *Arch. Int. Med.* 54: 436, 1934.
2. Birnbaum, W., Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-angiitis Obliterans, *Arch. Int. Med.* 53: 410, 1934.
3. De Blasì, A.: I Riperti di autopsia nel morbo di Buerger, *Pathologica* 26: 258, 1934.
4. Brofeldt, S. A.: Pathologisch-anatomische und klinische Studien über die Extremitätennekrose, *Acta Soc. med. fenn. duodecim.* 14: 6, 1932.
5. Buerger, L.: *The Circulatory Disturbances of the Extremities*, Philadelphia and London, 1924, W. B. Saunders Co.
6. Cserna, S.: Arteritis obliterans mit analogen Veränderungen in den Venen, *Wien. Arch. f. inn. Med.* 12: 213, 1926.
7. Van Donsen, E.: Maladie de Buerger avec atteinte des coronaires. Relation du deuxième cas connu, *Commentaires, Bruxelles-méd.* 15: 104, 1934.

8. Dürk, H.: Ueber pathologisch-anatomische Grundlagen plötzlicher Todesfälle, München. med. Wehnschr. 78: 627, 1931.
9. Ehrström, M. Ch.: Organiska hjärtsjukdomar vid thromboangiitis obliterans och vid Raynaud's syndrom, Finska läk-sällsk. handl. 75: 892, 1933.
10. Goecke, H.: Zur Entstehung der Entarteritis obliterans, Virchows Arch. f. path. Anat. 266: 609, 1928.
11. Jäger, E.: Zur pathologischen Anatomie der Thromboangiitis obliterans bei juveniler Extremitätengangrän, Virchows Arch. f. path. Anat. 284: 526, 1932.
12. Karsner, H. T.: Coronary Arteriosclerosis. Arteriosclerosis in E. V. Cowdry's, New York, 1933, The Macmillan Co.
13. Lemann, I. I.: Coronary Occlusion in Buerger's Disease (Thrombo-angiitis Obliterans), Am. J. M. Sc. 176: 807, 1928.
14. Perla, D.: Forty-One Cases of Thrombo-angiitis Obliterans With a Report of a Case Involving the Coronaries and the Aorta, Surg. Gynec. Obst. 41: 21, 1925.
15. Saphir, O.: Involvement of Medium-Sized Arteries Associated in the Syphilitic Aortitis, Am. J. Path. 5: 397, 1929.
16. Saphir, O., Priest, W., Hamburger, W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, AM. HEART J. 10: 567 and 762, 1935.
17. Telford, E., and Stopford, S. B.: Thrombo-angiitis Obliterans, Brit. M. J. 1: 863, 1935.

## CARDIAC PSYCHOSES AND NEUROSES\*

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**N**EUROPSYCHIATRY is a specialized but an inseparable part of internal medicine. In no branch of internal medicine are neuropsychiatric manifestations so common as in the diseases of the cardiovascular apparatus. Neurotic and psychotic symptoms frequently develop in the course of, and are causally related to, organic heart disease, the *cardiac psychoses*. On the other hand, there are a great many cases showing marked cardiac symptoms but without any primary cardiac disease, the so-called *cardiac neuroses*.

The purpose of this presentation is to discuss two types of conditions, cardiac psychoses and cardiac neuroses, with special emphasis on their most difficult aspect, that of treatment.

### CARDIAC PSYCHOSES

Behavior disorders and frank psychotic reactions are fairly common in the course of organic heart disease. These vary in intensity and depend upon a number of different causes.

The behavior disorders, commonly seen, are attributable to restricted activity, imposed by cardiac disease in adults, and especially in children (Foster<sup>1</sup>).

The *frank psychotic* reactions occurring in the course of heart disease vary from brief periods of mild delirium to outspoken dementia. The type of reaction depends upon the prepsychotic make-up of the individual and certain exciting causes. Thus one occasionally observes, in individuals with definite constitutional predispositions, manic, depressive, paranoid, and other schizophrenic reaction types. More common and more characteristic, however, are the *organic reaction types*. The latter are characterized: (a) in the intellectual sphere, by marked fluctuation of attention, difficulty in retention and activation of memory, defects in orientation, illusions and hallucinations, and impairment of comprehension and judgment; (b) in the affective sphere, by emotional instability; and (c) in the sphere of character, change to a type of conduct foreign to the individual's natural disposition.

The symptoms most commonly observed include states of confusion with disorientation, hallucinosis, persecutory trends, and states of psychomotor excitement.

The organic reactions may overshadow the underlying constitutional tendencies and bring about a complicated clinical picture. It is to be

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stressed, however, that the organic reactions may occur in previously well-integrated average normal personalities and are usually traceable to the exciting causes.

The exciting causes (Riesman<sup>2</sup>) include: (a) toxic factors due to renal toxemias, acidosis, and drugs, especially digitalis. I have observed a number of cases due to excessive, and especially the combined, use of two or more of the following agents: bromides, barbiturates, amidopyrine and the opiates. (b) Disturbance of circulation resulting in anoxemia, incident to congestion and edema, and in small areas of softening, which may be unaccompanied by focal brain signs, due to arteriosclerosis, thrombosis, and embolism. (c) Reflected pain from the diseased viscus, which, according to Head,<sup>3</sup> is responsible for the occurrence of transient and more or less lasting psychotic episodes (mood changes, suspicions, hallucinations).

The intensity, duration and prognosis of the psychotic reaction depend upon the underlying predisposing and exciting causes. In a previously well-integrated individual, a psychotic reaction even of moderate severity, when due solely to drug intoxication, will clear up in a few days to a few weeks with proper treatment. In the same type of individual, a psychotic reaction due to renal toxemia and cerebral vascular change may be a terminal process or may result in only temporary or incomplete recovery, with frequent recurrences and chronic mental invalidism. In the individual with a psychopathic make-up, trifling exciting causes may invoke lasting psychotic episodes and the severer causes may induce severe psychotic reactions leading to fatal cardiac failure.

The *treatment* of cardiac psychotic reactions includes: (1) the removal or reduction of exciting causes. In this connection it is well to remember the sensitivity of some individuals to the various sedatives and somnifacients, the cumulative effects of bromides, and, especially, the sensitivity of some individuals to combinations of drugs such as amidopyrine and phenobarbital. Disturbances of cerebral circulation may depend upon congestive failure, which should receive attention. When occlusions of small vessels are suspected, potassium citrate early and the iodides later may prove of value in some cases. (2) Some form of regimen and psychotherapy which will depend upon the type and severity of the psychotic reaction and of the associated cardiac condition. In this connection it is well to remember the danger of self-injury resulting from delirium or emotional depression and the need of proper supervision and at times of actual restraint.

#### CARDIAC NEUROSES

Subjective symptoms referable to the heart are observed in one form or another in nearly all neuroses. In some neuroses the cardiac complaint is a prominent or lasting symptom; in others it may be an acces-

sory complaint or only an ephemeral occurrence. The term "cardiac neurosis" implies a series of complaints referable to the precordium or to cardiac rate or rhythm constituting the predominant part of the clinical picture of the neurosis. "Cardiac neurosis," therefore, is only a part of the total situation—the neurosis—and can hardly be understood without an understanding of the concepts of neuroses in general.

Our concept of neuroses begins with the proposition that every disease must be considered as having both a somatic and a psychic component. The two components are indivisible and should be evaluated in their relation to etiology and to the total situation (Weisenburg, Yaskin, and Pleasants<sup>4</sup>). Whether the disease arises as a result of structural changes in the soma, of abnormal chemisms, or of emotional conflicts or abnormal psychic tensions, a change of affect of the individual (the subjective phase) and corresponding changes in the neuromuscular, autonomic-visceral, and secretory functions (objective evidences—emotional expression) take place. The principal relay station for emotional components of the various diseases would appear to be the diencephalon (Yaskin,<sup>5</sup> Fetterman<sup>6</sup>). It is responsible for the correlation of psychic and somatic disorders, has a regulating influence upon both of the major divisions of the vegetative system and indirectly upon most of the endocrine glands, upon metabolism, and heat regulation, and receives impulses from, and sends them to, the old and new brain and the neuraxis. In primary somatic disease this center receives abnormal impulses and registers them in the viscera, especially in the abdomen, "sounding board of emotions" (James<sup>7</sup>) in the form of emotions. In disorders of the general chemism the center may be affected, directly or centripetally via the vegetative nervous system. In states of emotional conflict and abnormal tension this center may be influenced from the cerebral cortex and then set up impulses responsible for *secondary* changes in function and even structure of the various viscera (Alvarez,<sup>8</sup> Moschcowitz,<sup>9</sup> Weiss<sup>10</sup>). Viewed from this concept, the diagnosis of neurosis or psychoneurosis requires not only the absence of any *primary* somatic or chemical disease, but also at all times the finding of a satisfactory psychogenic cause.

The above two criteria for the diagnosis of minor psychoses make such a diagnosis very difficult. The coexistence of organic heart disease and neurotic symptoms is well known, and their etiological relationship is often difficult to evaluate. Even with very painstaking investigation, organic disease may not be correctly diagnosed and the cases managed as neuroses. The causes for such errors have been reviewed elsewhere (Weisenburg, Yaskin, and Pleasants;<sup>4</sup> Yaskin<sup>11</sup>). Even more difficult, however, is the finding of adequate psychogenic causes without which therapy is often futile. The chief reason for the difficulty is that our present psychopathology is definitely unsatisfactory and, when subjected to scientific criteria of proof, is not completely convincing even to the

most sympathetic observer with the objective method of thinking. However, there is general agreement that for therapeutic purposes the diagnosis of psychoneuroses and neuroses implies the absence of any primary structural or chemical disease; the existence, in the majority of cases, of a certain constitutional make-up (the predisposing causes), the occurrence of precipitating or exciting causes, and the formation of symptoms which may be in the psychic or in the physiological sphere or in both. The constitutional factors may be inherited or acquired, frequently as an integral part of the psychosexual development of the individual. The term "psychopathic personality" is intended to describe in this presentation a type of make-up, characterized by either marked swings of mood or seclusiveness, misinterpretiveness, and other schizoid trends. In the "neurotic personality" the neurosis is "built into the character" and is characterized by manifestations intermediate between normal character traits and neurotic symptoms (Jones<sup>12</sup>). Symptom formation results from the action of some exciting cause which may be an injury, infection, a chemical disturbance, or some emotional stress. The symptoms may continue long after the exciting cause ceases to operate, and thus represent release phenomena of the neurotic traits of the previously apparently well-integrated personality. These symptoms include either frank anxiety states or symptoms tending to avoid anxiety such as conversion, compulsive-obsessive and neurasthenic syndromes, etc. (Yaskin<sup>5</sup>). These symptoms may vary in severity from a slight headache, increased fatigability and irritability, to devastating visceral disturbances, intractable insomnia with marked agitation, and alarming loss of weight. The clinical manifestations frequently overshadow completely the primary constitutional factors or the immediate precipitating mechanisms.

Anxiety is the central symptom of nearly all the neuroses and psychoneuroses and is of fundamental importance in the management of cardiac neuroses. Anxiety may be defined as a form of affectivity recognized introspectively as an unpleasant affect, accompanied by a fear, without any, or without an adequate cause, and manifested objectively by abnormal changes in the neuromuscular, autonomic, and secretory functions (emotional expressions). That the heart should respond to states of fear is not surprising when it is borne in mind that, like the gastrointestinal tract, this organ has a rich sympathetic and parasympathetic innervation and that the vegetative system is under the control of the central nervous system. In addition, Cannon<sup>13</sup> has shown that, under the influence of emotions, there is an alteration in the epinephrine content which is particularly prone to influence the accelerators of the heart.

The cardiac symptoms differ in the various *types* of neuroses and are best discussed under several headings as revealed in a recent study of 100 cases (Yaskin<sup>14</sup>).



Table I indicates family and personality; Table II, the precipitating causes; Table III, the modes of treatment employed; and Table IV the end-results.

TABLE I

## FAMILY HISTORY AND PERSONALITY IN THIS SERIES OF 100 CASES

FAMILY HISTORY	NO. OF CASES	PERSONALITY	NO. OF CASES
Neuropathic	44	Neurotic	75
Psychopathic	16	Psychopathic	2
Negative	40	Average normal	23
Total	100	Total	100

TABLE II

## THE PRECIPITATING CAUSES IN THIS SERIES OF 100 CASES

	ANXIETY NEU- ROSIS	CONVER- SION HYS- TERIA	ANXIETY HYS- TERIA	COMPUL- SIVE- OB- SESSIVE RE- ACTIONS	OCCUR- RENCE IN NUM- BER OF CASES
Financial reverses and economic insecurity	2	5	6	2	15
Illness and death in immediate family and of close friends	2	2	12	1	17
Marital infelicity, including infidelity		5	12		17
Other dissensions in family		3			3
Fear of criminal punishment and social ostracism to self or to members of family			4		4
Surgical menopause and other endocrine disturbances		1	2	1	4
"Old maidness"			5		5
Abnormal attachment to certain members of family			5	5	10
Coitus interruptus and other unsatisfactory methods of contraception	4				4
Fears related to masturbation	3				3
Fears of marriage and pregnancy	1		4		5
Frigidity			8	3	11
Impotence			3		3
Incest with sisters				2	2
Homo-sexual trends	1		6	3	10
Anal eroticism				5	5
Sodomy				2	2
Ordinary strain of life and no satisfactory causes			9		9

## CARDIAC SYMPTOMS IN THE VARIOUS TYPES OF NEUROSES AND PSYCHONEUROSES

*Anxiety Neurosis.*—Under this heading are included those neuroses characterized by *episodic* occurrence of anxiety, accompanied by definite somatic symptoms, and by *complete* or *nearly complete* freedom from all symptoms between attacks. Of all somatic manifestations, palpita-

tion is the most common. Its occurrence is accompanied by anxiety, trembling, and general weakness and is frequently accompanied or followed by perspiration. There were 9 cases of anxiety neurosis in the above mentioned series of 100 cases. In each of these cases palpitation with anxiety was the outstanding symptom complex. The personality make-up in anxiety neurosis is not of particularly great significance.

TABLE III

## MODES OF TREATMENT IN THIS SERIES OF 100 CASES

	ANXIETY NEUROSIS	CONVERSION HYSTERIA	ANXIETY HYSTERIA	COMPULSIVE- OBSESSIVE REACTIONS	TOTAL NUMBER OF CASES
Encouragement	4	4	30	2	40
Suggestion	4	9	48	5	66
Rationalization and persuasion	3	2	10	2	17
Attempts at compromise formation		3	25	2	30
Education and reeducation			12	2	14
Partial analysis		4	15	11	30
Partial analysis with amytal narcosis				2	2
Regimen at home, at work, and change of environment other than hospitalization		2	11		13
Hospitalization			11		11
Occupational therapy			7		7
Physiotherapy			6		6
Sedative and tonic medication	5	3	43	6	57
Appropriate contraception	6				6

TABLE IV

## END-RESULTS IN THIS SERIES OF 100 CASES

	ANXIETY NEUROSIS	CONVERSION HYSTERIA	ANXIETY HYSTERIA	COMPULSIVE- OBSESSIVE REACTIONS	TOTAL NUMBER OF CASES
Recovery	9	9	21	2	41
Improvement		3	30	8	41
No improvement			6	3	9
Developed psychoses			6		6
Recurrence	1	2	18	3	24

The precipitating causes are to be found in the immediate present or in the recent past and, as observed in this series, were not particularly complicated. The treatment in this group of cases is relatively simple if the causes can be removed. Inasmuch as most of the latter are to be found in the irregularities of the sexual act, the treatment consists largely in the removal of the cause, in suggestion, encouragement, and other superficial modes of psychotherapy, and in sedative medication.

The results in the majority of cases of anxiety neurosis are favorable and all cases in this series recovered, there being only one recurrence.

*Conversion Hysteria.*—Under this term are designated forms of psychoneuroses characterized by the presence of motor, sensory, visceral, and episodic phenomena (conversion symptoms) accompanied by little or no anxiety, not due to any physical or biochemical abnormality, and traceable to some definite psychogenic cause. Cardiac complaints are not prominent symptoms in conversion hysteria and consist of a complaint of vague precordial pains or of a statement by the patient that he has "heart disease" but unaccompanied by any overt anxiety. In 12 patients in this series, 2 complained of heart weakness, 1 of precordial pain, and 2 of "cardiac disease." As revealed in the four tables, in conversion hysteria the family history and the personality of the patient play a considerable rôle. The precipitating causes in this group of cases are usually not difficult to find, and in this series were related chiefly to marital difficulties, death in the family, or to a feeling of economic insecurity. Suggestion in some form is probably the first method of treatment to be employed in these cases. Attempts at compromise formation in marital and economic difficulties also require and deserve considerable attention. The end-result in these cases is usually good providing the cause can be removed or the patient is made to make some compromise. In this series 9 patients recovered, 3 improved, and only 2 had recurrences.

*Anxiety Hysteria.*—Under this term are designated conditions showing a variety of somatic complaints not due to primary organic or biochemical disturbances, accompanied by diffuse anxiety or by phobic phenomena, and traceable to psychogenic, often unconscious, causes. In anxiety hysteria cardiac complaints are fairly constant and often severe. The anxiety hysteria group comprised 63 per cent of the series of 100 cases analyzed. In these 63 cases changeability of pulse rate and frequent attacks of tachycardia were observed in 43 cases, actual dyspnea in 13, precordial discomfort in 24, dizziness and especially fear of cardiac death in 18, transient elevation in blood pressure in 17, and fear of being left alone or going out unaccompanied in 13 cases. Three of these patients had previously been subjected to subtotal thyroidectomy without any improvement of symptoms.

In this group of cases the family histories indicate a large proportion of neuropathic and psychopathic ancestry. The personality histories indicate a large neuropathic element. The predisposing causes in this group of cases are usually deep-seated, while the precipitating factors are numerous and varied. Even without a deep analysis and only by the review of the precipitating factors, it may be observed that these patients have a great deal of distortion in their psychosexual development and attitude. As is well known, the clinical course of these cases is extremely troublesome to the patient, the family, and to the physician.

In addition to numerous somatic complaints, the presence of diffuse anxiety, and numerous phobic phenomena make the management of these cases trying and require a great deal of ingenuity on the part of the physician and his aides. Eleven of this series required hospitalization because it was impossible to manage them at home. In another 11 cases a great deal of attention had to be paid to the regimen and the daily activities of the patients, which were outlined for them. Encouragement, suggestion, and hospitalization were used in a good many of the cases but these in themselves have limited value. An element which is of some importance in the treatment of these patients is an attempt at compromise formation. Especially is this true in cases of marital difficulties where the illness of the patient is probably the most important element in the marital infelicity. Sedative and tonic medication were indispensable in most of these cases. Perhaps the single most important therapeutic agent is the partial analysis, but, because of the elements of time consumption and expense and because of the resistance of a good many patients, this is not always practical. My impression is that, of all the cases, those in whom partial analyses were performed were most benefited. At the same time attention is directed to the fact that, even in those 15 cases where partial analysis was employed, other forms of treatment, especially sedative and tonic medication, were used.

In this series of 63 cases, 21 recovered, 30 improved, and 6 showed no improvement. Eighteen of the series had recurrences. Thirteen of the 21 recovered patients received a partial analysis. It is of interest to note that among the recurrences not one had received partial analysis. Six patients developed psychoses, which should make the diagnosis of anxiety hysteria guarded. Five of these six cases developed an agitated depression while one turned out to be definitely schizophrenic.

*Compulsive-Obsessive Reactions* (Psychasthenia of Janet).—Under this term are designated conditions characterized by the existence of irrepressible thoughts and irresistible impulses designed to avoid anxiety, by the patient's recognition of the absurdity of these thoughts and impulses, and by the appearance of anxiety when the patient attempts to "disobey" the thoughts and impulses. Palpitation and a feeling of impending death is the penalty in these patients when they attempt to disobey the irrepressible thought or impulse. There were 13 cases in the analyzed series. In this group the family history is not predominantly significant. The personality history, on the other hand, shows a very definite neuropathic trend. This becomes more evident when even a partial analysis is attempted. By this method neurotic traits are found to have existed since childhood, but were thoroughly integrated in the personality make-up, and did not produce disabling symptoms until somewhat later in life. The precipitating causes can be ascertained only by a partial analysis and then are to be found largely in the

psychosexual sphere. It is in this form of psychoneurosis that treatment other than a partial analysis is of little value. These patients do have, however, periods of anxiety, when the ordinary forms of treatment including encouragement, suggestion, and sedative medication are of definite value. For the majority, however, some attempt must be made to make them relive their early experiences. This is a long-drawn-out affair because of the inherent resistance of these patients to the necessary investigation and because of their critical attitude toward any form of treatment. Of the 13 cases in this series all received a partial analysis, two with the aid of amytal narcosis (Yaskin<sup>15</sup>).

*Neurasthenia.*—By this term is understood a relatively rare disease beginning in early life, lasting with intermissions throughout life, and characterized by abnormal mental and physical fatigability and irritability, various somatic complaints, mental depression, and insomnia. Neurasthenia as a primary disease is to be distinguished from the neurasthenic symptom-complex which is of common occurrence in many and varied somatic, endocrine, and metabolic diseases as well as in the psychoses, neuroses, and psychoneuroses. In this series there were only 3 cases, all with a neuropathic family history, and all showing temporary improvement with suitable rest regimens and living within the bounds of their physical and mental capacities. In the 3 patients analyzed, palpitation, precordial discomfort, and "heart consciousness" were found. The analysis of the cases of neurasthenia is omitted from the tables.

#### GENERAL COMMENT ON THE CARDIAC NEUROSES

It is evident that cardiac complaints are nearly universal in all forms of neuroses and constitute the predominant and lasting symptoms in some. The character, severity, and duration of cardiac symptoms depend upon the type of neurosis of which the cardiac symptom is only a constituent part. The type of the neurosis depends upon the various etiological factors which are responsible for the mechanism of symptom formation. In the final analysis the diagnosis and successful treatment of cardiac neurosis depend upon our ability to determine the etiological factors. This is not always easy.

The *family history and personality* (as indicated in Table I) are of some interest. The high incidence of neuropathic inheritance is in keeping with the civilian types of psychoneuroses. The incidence of the neurotic types of personality in this series is higher than is generally supposed to be the case in the psychoneuroses. An important reason for this probably is the fact that 32 of the 100 cases received a partial analysis thus making it possible to disclose the existence of neurotic traits prior to the development of the clinical manifestations.

The *precipitating causes*, as shown in Table II, are of definite importance. In keeping with the general knowledge on this subject, there are no specific etiological factors. The causative factors embrace a wide

range of economic, social, marital, and psychosexual components. In anxiety neurosis and conversion hysteria the causes are relatively superficial, while in anxiety hysteria and compulsive-obsessive reactions they are more profound and are more intimately associated with the psychosexual life. The latter observation is, however, definitely influenced by the fact that 15 of the 63 patients with anxiety hysteria and all of the 13 patients with compulsive-obsessive reactions received partial analysis while only 4 of all the remaining patients in the series of 100 were partially analyzed.

In the majority of cases in this series there is more than one precipitating cause, and it is probably true that the clinical manifestations result from the cumulative action of various factors. It is frequently impossible to evaluate the importance of several existing causes. This is true even when a careful personality study is combined with an accurate chronological determination of the development of the various precipitating factors.

At times it is difficult to state whether the "precipitating cause" is really a cause or only an evidence of disease. This is particularly true of marital infelicities which are not infrequently determined by the subtle neurotic attitudes of the patient. If this be so, it is of considerable therapeutic importance, especially as it points to the necessity of attempting compromise formations. In a large proportion of the 17 cases of marital infelicity in this series, the neuroticism of the patient was the determining cause of the marital discord.

It would appear from this review that, contrary to psychoanalytical trends, ego and herd instinct motivations, as observed in economic insecurity, fears of criminal punishment and of social ostracism, "old maidness," and similar related factors play an important rôle as precipitating causes in the psychoneuroses. On the other hand, there is a large proportion of patients in whom the disturbance of the love life undoubtedly acted as a determining cause. The shades of the disturbance varied from infidelity of a spouse to sister incest. It is particularly significant that frigidity was encountered in 11 cases and homosexual trends in 10 cases, and these occurred almost exclusively among the cases found in the anxiety hysteria and compulsive-obsessive reaction groups.

The *modes of treatment* employed, as shown in Table III, permit of no definite conclusion although there are many interesting factors. The methods employed are clinical applications and are not to be regarded necessarily as scientifically controlled procedures. They are therefore not entitled to scientific credit nor to scientific criticism. As empiric measures, their value should be judged entirely by their therapeutic success or by their failure.

A mere glance at Table III discloses that a great many methods were used in the same patient, and one unpleasantly associates this with the

old "polymorphous pharmacy." Like the latter, however, these methods have, for the present, some definite though empiric value.

Irrespective of the fundamental psychopathology, the relief of symptoms is always of importance. Some methods, such as encouragement and suggestion, are, like the stomachics and hematinics of old, of distinct benefit in the majority of cases. Encouragement was employed in 40 and suggestion in 66 of the 100 cases. These methods are intended for the removal or correction of symptoms and are particularly valuable in conversion hysteria and in most cases of anxiety hysteria. They are of limited value in some cases of anxiety hysteria and only rarely of real benefit in compulsive-obsessive reactions. Of the other methods intended for the amelioration of symptoms, regimen and hospitalization were used in 24 cases, most of which were anxiety hysterias. In some cases these methods were indispensable and, in the majority of others, of definite benefit. Along with these procedures, occupational and physical therapy proved useful. Somnifacients and sedatives were employed without hesitancy when anxiety was a prominent or acute symptom in any of the cases of this series. In the ill-nourished patients, tonics were used freely.

The remaining methods which were employed attempt to influence the underlying causes and psychopathological processes. Mention should be made that most of these methods are tinted with elements of suggestion and encouragement, a fact which need not detract from their therapeutic value.

Appropriate contraception is frequently a relatively simple and beneficial procedure, especially in anxiety neurosis.

Rationalization and persuasion, education and reeducation, all of which attempt to utilize the intellectual approach, are probably of limited value as observed in most cases in which they were used. They were employed chiefly in anxiety hysteria and perhaps were useful in preparing the patient for a partial analysis. Rationalization and persuasion are of some benefit in anxiety neurosis resulting from the fear of the consequences of masturbation.

An attempt at compromise formation is of definite benefit in suitable cases. In this procedure, the patient is carefully guided to evaluate the various situations which may have a bearing on his illness. By comparing different possible solutions in regard to their possible consequences, the patient makes a choice in accordance with the changed emotional attitude. This process is tedious but is of considerable benefit to the patient. Attempts at compromise formation have proved of definite value in some cases of marital infelicity, in situations associated with a feeling of economic insecurity, "old maidness," fear of ostracism, and in related conditions. The great majority of cases treated by this method were anxiety hysteria.

Partial analysis is, in the author's experience, the best psychotherapeutic approach to the underlying psychopathology and etiological factors. By this method a limited exploration of the unconscious is attempted, first, through formal interviews, then, after some explanation to the patient of what is sought, by a modified free association technic. This method is not to be confused with a full psychoanalysis. It is not a complete investigation of the unconscious but, surprisingly, it is often deep enough to touch upon fundamental processes and achieve considerable benefit. It has the great advantage over complete analysis of not being so time consuming. It proved of definite benefit in most of the cases of conversion hysteria, anxiety hysteria, and compulsive-obsessive reactions in which it was used. In the last named group it is the only method (except complete psychoanalysis) that is worth attempting. In two cases each treatment was preceded by a light sodium amytal narcosis.

The end-results, as shown in Table IV, compare rather favorably with end-results of treatment in many other branches of medicine. The present review does not permit any formulation as to what determines these end-results. In general, it may be stated, however, that the outcome of the treatment is definitely influenced by the type of the neurosis and the modes of treatment.

Most recoveries were attained in the anxiety neuroses in which the causes could be effectively influenced, and least in the compulsive-obsessive reactions which are accompanied by deep, resistive psychosexual distortion. It is generally agreed that the latter are not uniformly cured even by prolonged psychoanalyses. The recoveries in conversion hysteria, treated chiefly by suggestion and encouragement, were good. The recoveries in anxiety hysteria were better than was anticipated, and the majority of the recoveries in this group were attained by partial analysis and attempts at compromise formation.

Improvement was observed chiefly in anxiety hysteria and in compulsive-obsessive reactions. In the former group the results were due to a combination of several methods among which regimen and hospitalization played a large, though not an exclusive, rôle. In the latter group the improvement was due solely to partial analysis.

The failure of improvement in 9 cases, 6 anxiety hysteria and 3 compulsive-obsessive states, is to be ascribed to the severity of the clinical condition, the failure of cooperation or actual resistance on the part of the patient, and probably, what is most important, to a lack of therapeutic acumen on the part of the physician.

Six patients developed psychoses. This probably was not due to faulty therapy, but to poor diagnostic judgement.

Recurrence was observed in 24 cases, 18 of which were anxiety hysteria. The recurrences were traceable in the majority of cases to the incidence of new or reactivated precipitating causes, and, in many instances, to inadequate treatment of the preceding attack.



## SUMMARY AND CONCLUSIONS

Psychotic reactions in the course of organic heart disease vary from mild behavior disturbances to severe reactions. The type and severity of the reaction depend upon the prepsychotic personality, upon renal toxemia, acidosis, drugs, cerebral anoxemia associated with congestion, edema and small softening, and in some cases upon enforced inactivity and reflected pain.

The term "cardiac neurosis" implies a series of complaints referable to the precordium or to cardiac rate and rhythm. These complaints are only a conspicuous part of the total neurosis. Anxiety is the central problem of all neuroses and psychoneuroses. The etiology and symptomatology of the cardiac neuroses vary with the several types of neuroses and psychoneuroses.

One hundred cases comprising anxiety neuroses, conversion hysteria, anxiety hysteria, compulsive-obsessive reactions, and neurasthenia were reviewed from the standpoint of cardiac symptoms, family history, personality, precipitating causes, modes of treatment, and end-results.

This study is an attempt to emphasize that cardiac neuroses should be managed as neuroses and psychoneuroses. As such they require comprehensive neuropsychiatric studies and utilization of various therapeutic approaches.

## REFERENCES

1. Foster, N. B.: Psychic Factors in the Course of Cardiac Disease, *J. A. M. A.* 89: 1017, 1927.
2. Riesman, D.: Acute Psychosis Arising During the Course of Heart Disease, *Am. J. M. Sc.* 161: 157, 1921.
3. Head, Henry: Certain Mental Changes That Accompany Visceral Disease, *Gaulstounia Lectures for 1901, Part III, Brain* 24: 345, 1901.
4. Weisenburg, T. H., Yaskin, J. C., and Pleasants, Henry: Neuropsychiatric Counterfeits of Organic Visceral Disease, *J. A. M. A.* 97: 1751, 1931.
5. Yaskin, J. C.: The Psychobiology of Anxiety, *Psychoanalyt. Rev.* 23: Supp. 1-24, 1936.
6. Fetterman, J. L.: The Correlation of Psychic and Somatic Disorders, *J. A. M. A.* 106: 26, 1936.
7. James, Wm.: *Principles of Psychology* 2: 449, 1927, New York, Henry Holt & Co., Inc.
8. Alvarez, W. C.: Ways in Which Emotions Can Affect the Digestive Disturbances, *J. A. M. A.* 92: 1231, 1929.
9. Moscheowitz, Eli: The Psychogenic Origin of Organic Disease, *Arch. Neurol. & Psychiat.* 32: 903, 1934.
10. Weiss, E.: The Management of Patients With Essential Hypertension, *Pennsylvania M. J.* 39: 313, 1936.
11. Yaskin, J. C.: A Review of Some Errors in Neuropsychiatric Practice, *M. Times & Long Island M. J.* 59: 417, 1931.
12. Jones, Ernest: The Anxiety Character, *Medical Review of Reviews* 36: 177, 1930.
13. Cannon, W. B.: *Bodily Changes in Pain, Fear, and Rage*, New York, 1929, D. Appleton and Co., pp. 1-192.
14. Yaskin, J. C.: Psychoneuroses and Neuroses: A Review of 100 Cases With Special Reference to Treatment and End-Results, *American Journal of Psychiatry*, July, 1936.
15. Yaskin, J. C.: The Treatment of Spasmodic Torticollis With Special Reference to Psychotherapy, With a Report of a Case, *J. Nerv. & Ment. Dis.* 81: 299, 1935.

## THE TREATMENT AND THE IMMEDIATE PROGNOSIS OF CORONARY ARTERY THROMBOSIS (267 ATTACKS)\*

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IN THIS country and abroad the mortality rate of coronary artery thrombosis is quoted generally as ranging from 35 to 65 per cent with an average of 50 per cent.<sup>1-9</sup> Dublin<sup>10</sup> has stated, "No other disease in the entire field of medicine with the possible exception of cancer offers so large an opportunity for life-saving service." Our experience leads us to believe that the mortality may be lessened by certain simple logical procedures and by the use of a low calorie diet.

Coronary artery thrombosis usually presents a characteristic picture. Occasionally, however, the differentiation from other conditions, particularly angina pectoris, is difficult. If the diagnosis is doubtful the patient should be treated as though he had suffered a coronary artery occlusion. He should be put to bed and a search patiently made for a drop in blood pressure, a change in heart sounds, alterations in the electrocardiogram, etc. These signs may not appear for a few days or longer, but within two to four days one can usually make certain whether a real closure of a coronary artery has occurred.

The data we are analyzing were collected from both private and ward patients. The number of attacks observed was 267, of which 122 occurred in 103 private patients (A.M.M.) and 145 in 140 hospital patients. No case was included unless the diagnosis of acute coronary artery occlusion was certain.

### TREATMENT

It should be understood that the procedures described are for the period of the acute coronary artery thrombosis. When this diagnosis was made or suspected, the patient was put to bed immediately. Absolute quiet and rest were enjoined. In private practice day and night nurses were employed whenever possible, but hospital patients had floor nursing care only; this included being fed whenever possible. There was no hesitancy in administering as much as  $\frac{3}{4}$  grain of morphine within twelve hours if pain was very severe. Practically every clinician who has studied coronary thrombosis has advocated the use of this drug. We think morphine is of help not only because it relieves pain but also

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because, as David<sup>11</sup> has indicated, it lightens the work of the heart by slowing the heart rate and lowering the basal metabolism. Morphine diminishes respiratory effort and tends to prevent nocturnal dyspnea and cardiac asthma as Eppinger and his coworkers,<sup>12</sup> Fraser,<sup>13</sup> and Harrison<sup>14</sup> have shown.

*Diet.*—Diet was an important part of the treatment. Very little food was given during the first few days, especially to the very sick patients. The fluids were limited to 1,000 to 1,200 c.c. unless the patient was perspiring profusely. When nausea or vomiting was present, food was withheld and small quantities of cracked ice and charged water were given. As the patient improved, the diet was slowly increased so that in from five to seven days he was receiving 750 to 850 calories. The diet was well balanced, containing approximately 100 gm. carbohydrate, 50 gm. protein, 20 gm. fat with adequate vitamins and calcium.

#### 800 CALORIE DIET

<i>Breakfast</i>	<i>Sample Menu</i>
100 gm. 12 per cent fruit	$\frac{1}{2}$ medium orange
10 gm. cereal	2 tablespoons cooked cereal
200 c.c. skimmed milk	1 cup
1 egg	1 egg
15 gm. bread	$\frac{1}{2}$ slice
<i>Dinner</i>	
60 gm. meat	2 ounces meat
100 gm. 3 per cent vegetable	$\frac{1}{4}$ cup spinach
100 gm. 12 per cent fruit	3 plums
15 gm. bread	$\frac{1}{2}$ slice
200 c.c. skimmed milk	1 cup
<i>Supper</i>	
1 egg	1 egg
100 gm. 3 per cent vegetable	$\frac{3}{4}$ cup canned string beans
100 gm. 12 per cent fruit	1 medium peach
15 gm. bread	$\frac{1}{2}$ slice
200 c.c. skimmed milk	1 cup

The 800 calorie diet was maintained for at least three to six weeks and frequently for much longer periods. Obviously, adherence to the diet prescribed was necessary if any conclusions were to be drawn as to the value of this form of therapy. A patient presumably on an 800 calorie diet might actually be ingesting several hundred calories more because of a kind attendant or relative. Our procedure was explained to the patient and his family; indeed the cooperation of the latter was essential. An endeavor was made to accord each patient individual attention and to satisfy his tastes whenever possible. In only a minority of cases did the patient complain of hunger; this could usually be allayed by arranging for a small evening portion or by the addition of nonealoric candy, etc. Increasing the bulk of the food with vegetables sometimes sufficed. Although only very exceptionally did we find it necessary to increase the caloric intake in our cases, we were ready to do it if it was indicated in a particular case.

*Drugs.*—Digitalis, nitroglycerin, amyl nitrite, adrenalin and ephedrine were considered contraindicated. Fenn and Gilbert<sup>15</sup> believed that digitalis increased precordial pain. Experimentally it has been shown to be harmful, for Bellet, Johnston, and Schechter<sup>16</sup> found that dogs in which myocardial infarction had been produced were more susceptible to fatal digitalis poisoning.

In regard to nitroglycerin, Hadfield<sup>17</sup> found that by lowering diastolic blood pressure in dogs he could increase the size of the experimental infarct. Hence he, as well as Hubble<sup>18</sup> and also Luten,<sup>19</sup> concluded that nitroglycerin was dangerous in coronary occlusion. Prodger and Ayman<sup>20</sup> and Sprague and White<sup>21</sup> have cited clinical instances in which coronary thrombosis was precipitated or its course influenced fatally by nitroglycerin. Grollman<sup>22</sup> has proved that nitroglycerin increases the work of the heart. Riesman<sup>23</sup> on clinical grounds considered both digitalis and nitroglycerin dangerous.

Concerning the contraindication to the use of adrenalin, it is hardly necessary to enter into detail. Levine, Ernstone, and Jacobson<sup>24</sup> showed that adrenalin produced pain in patients with an anginal syndrome, and Cottrell and Wood<sup>25</sup> pointed out that it could cause other serious symptoms. Grollman<sup>22</sup> indicated that it, too, increased the work of the heart.

With congestive failure the usual measures were employed, that is, limitation of fluid and salt. We did not give digitalis but resorted to injections of mercupurin when necessary.

Cardiac arrhythmias exclusive of multiple premature beats occurred in twenty cases. These were nodal rhythm, paroxysmal tachycardia, auricular fibrillation, auricular flutter, partial and even complete heart-block. Except in one case of auricular fibrillation these severe irregularities disappeared spontaneously without any specific treatment.

No cathartics or enemas were given during the first three to five days. On the low diet described, there was rarely distention in spite of lack of bowel movement.

Oxygen therapy was utilized in thirty-five attacks occurring on the ward. In this group there were twenty-three deaths. This method of treatment was employed only in cases with cardiac failure or pulmonary complications, particularly in cases with severe dyspnea and cyanosis. It often relieves pain, dyspnea, and cyanosis. Occasionally, however, a patient was quite uncomfortable in the oxygen tent in spite of proper air conditioning and oxygen supply.

*Prolonged Stay in Bed.*—The patient was kept in bed from four to ten weeks, the average time being five and one-half weeks. He was then permitted gradually to get out of bed into a chair and usually by the seventh or eighth week he was able to walk. By lowering the energy required of the body, bed rest diminishes the work of the heart. Numerous writers have expressed the opinion that a stay of four to six weeks

in bed is essential. Bedford<sup>26</sup> and also Levine<sup>2</sup> have emphasized that only after the first three to six weeks does repair of the injured heart muscle set in. We believe that it is equally important for the patient's future health. The patient who leaves his bed too early is more likely to develop congestive failure or to have a recurrence of a coronary thrombosis. Cooksey<sup>8</sup> showed that patients who were permitted out of bed too soon did not fare as well as those who remained in bed for at least six weeks. Sutton and Davis<sup>27</sup> have shown experimentally in dogs that the longer the rest following infarction, the firmer the scar which results. In the dogs allowed to exercise early, aneurysmal dilatation through a thin scar resulted.

## RESULTS

In the 267 attacks studied by us the mortality rate in the first attack was 8 per cent (Table I). For all the attacks, it was 16.5 per cent. All deaths were included from the time of admission to discharge or,

TABLE I  
MORTALITY RATE OF EACH ATTACK OF CORONARY ARTERY THROMBOSIS

	HOSPITAL	PRIVATE	MALE	FEMALE	TOTAL
1st attack	78	74	112	40	152
Deaths	8	4	9	3	12
Mortality	10%	5.4%	8%	8%	8%
2nd attack	48	37	67	18	85
Deaths	14	5	16	3	19
Mortality	29%	13.5%	24%	16.5%	22%
3rd attack	18	8	22	4	26
Deaths	8	4	9	3	12
Mortality	44%	50%	41%		46%
4th attack	2	2	2	2	4
Deaths	0	1	0	1	1
Mortality					
All attacks	145	122	203	64	267
Deaths	30	14	34	10	44
Mortality	20.7%	11%	16.7%	15.6%	16.5%*

\*Excluding deaths occurring in the first 24 hours, the mortality was 11 per cent.

in the patients seen in private practice, up to the time of being permitted out of doors. If deaths occurring within twenty-four hours are excluded, the mortality rate was 11.5 per cent. Probably as a result of more prompt and meticulous medical and nursing care, the private patients fared better than those treated in the hospital. In the former the mortality rate was 5.4 per cent for the initial attack and 12 per cent for all attacks; in the latter, 10 per cent for initial attacks and 20 per cent for total (Table I). One may conclude, therefore, as Conner and Holt<sup>2</sup> have already pointed out, that the majority of patients survive their first coronary occlusion. Other authors, too, have indicated this; Moritz

and Beck<sup>28</sup> discovered at post-mortem examination that 86 per cent had survived their first occlusion. Barnes and Wade,<sup>29</sup> Saphir, Priest, Hamburger, and Katz,<sup>30</sup> Smith, Rathe, and Paul<sup>31</sup> found evidence of more than one coronary occlusion in the great majority of cases seen at autopsy.

The results were practically the same in men and women in all decades (Table II). In our series the ratio of men to women was three to one (Table II). Although some of the earlier reports on coronary thrombosis gave the impression that this disease is much more frequent in men, it is now evident that it is not uncommon in women. Moritz and Beck<sup>28</sup> in ninety-four post-mortem examinations actually found the number of men and women to be the same.

The ages of the patients studied ranged between twenty-seven and eighty-seven years (Table II). The average was fifty-four years for both men and women. The average age of those who died was fifty-seven years, which age is only slightly greater than the average age of those who recovered from attacks.

TABLE II

NUMBER OF ATTACKS OF CORONARY ARTERY THROMBOSIS IN EACH AGE GROUP

AGE IN YR.	MALE	FEMALE	TOTAL	DEATHS
27-39	15	6	21 (8%)	2 (10%)
40-49	46	16	62 (23%)	8 (13%)
50-59	70	16	86 (32%)	13 (15%)
60-69	53	18	71 (27%)	15 (21%)
70-87	19	8	27 (10%)	6 (22%)
Total	203	64	267	44

Twenty-one attacks were treated in patients under the age of forty; only two of these died. Sixty-two attacks were treated in patients between forty and forty-nine years of age, with a 13 per cent mortality. The mortality rate rose in the older age groups, reaching 22 per cent in the eighth decade. In each decade, men and women fared the same. It will be seen that coronary thrombosis is not uncommon between thirty and fifty or even between thirty and forty, as Conner and Holt<sup>3</sup> have pointed out, although it occurs most frequently in the sixth decade. Once more, in confirmation of these authors, our finding that the mortality rate is lowest in the young and higher in the older group does away with a more or less prevalent notion that coronary thrombosis is much more serious in the young, i. e., the fourth decade or earlier.

Multiple attacks of coronary thrombosis were surprisingly common. One hundred four (43 per cent) of our patients sustained more than one closure: there were two attacks each in 76 patients, three attacks each in 24, and four each in 4 patients, totaling 379 episodes of acute coronary artery occlusion in 243 patients, although only 267 of these attacks were treated by us. The same post-mortem evidence that was previously cited<sup>28-31</sup> to emphasize the fact that patients survived the

first attack of coronary thrombosis can be given to demonstrate the frequency with which multiple attacks occur. It is unusual to find evidence of only one myocardial infarct post mortem. When death occurs, proof of multiple coronary occlusion is present in nearly 80 to 90 per cent of cases.

Hypertension was present in 177 or 66 per cent of the attacks either at the time of observation or preceding the attack. If the systolic blood pressure was 150 mm. or more or the diastolic 90 mm. or more, hypertension was considered to be present. The mortality rate in these hypertensive patients was 13 per cent. In the ninety attacks without known hypertension, it was 23 per cent. Moreover, of the forty-four patients who died only 23 (52 per cent) suffered from hypertension. Thus the prognosis in our series was not directly influenced by the presence of hypertension.

The electrocardiograms were analyzed from the standpoint of localization of the infarct on the anterior or posterior surface of the heart.<sup>32, 33\*</sup> Both the electrocardiogram and the post-mortem studies were used for this localization. In patients suffering their initial attack of myocardial infarction, the infarction occurred on the anterior surface in sixty-five and on the posterior surface in sixty-six. The mortality rate in each group was about the same, 7.5 per cent and 6 per cent, respectively. In nineteen cases there was evidence of infarction of both surfaces, and the mortality in this group was 10.5 per cent.

In patients suffering an attack subsequent to the first, the last acute infarction occurred on the anterior surface in thirty-nine with a mortality of 18 per cent and on the posterior surface in forty with a mortality of 22.5 per cent. Infarction occurred on both surfaces in twenty-five, the mortality rate rising to 44 per cent. Hence, the frequency of anterior and posterior infarctions was about the same and mortality rate identical.

#### DISCUSSION OF THE UNDERNUTRITION THERAPY

We believe that the undernutrition therapy<sup>34-37</sup> has been a factor in the good results we are reporting, and we shall endeavor to give evidence to support this view.

During the two periods, 1930 to 1932 and 1933 to June, 1934, the mortality rate of ward patients at the Mount Sinai Hospital, New York, was 39.7 per cent and 40.5 per cent, respectively, whereas since June, 1934, under our method of treatment it has been only 20.7 per cent (Table III). Excluding deaths occurring in the first twenty-four hours, the mortality rate has been halved, i.e., from 33 per cent to 16 per cent,

\*R-T elevation, T-wave inversion and a large Q-wave in Lead I or Leads I and II, and R-T depression, upright T-wave, and absent Q-wave in Lead IV were evidences of infarction of the anterior surface of the left ventricle. R-T transition elevation, inversion of the T-wave and large Q-wave in Lead III or Leads II and III, and elevation of the R-T and upright T-wave in Lead IV were evidences of infarction of the posterior surface of the heart. In those cases, in which R-T elevation and T-wave inversions appeared in all leads, it was considered that infarction of both surfaces of the heart had occurred.

and considering the mortality of the first attack alone, the rate has actually decreased to less than one-third, i. e., from 36 per cent to 10 per cent. Yet the only change in the method of treatment in this latter period (1934-1936) had been the institution of undernutrition.\* Previously cardiac patients were given the ordinary hospital diet; indeed when a "cardiac" diet was specified, it was, as a rule, high carbohydrate, high calorie. It would, therefore, seem logical to conclude that our improved results may be due to undernutrition. It is particularly significant, we think, that the mortality rate of the first attack has been so conspicuously reduced, for it is during the initial attack that treatment would have the greatest effect on the outcome. After all, patients during their second or subsequent attacks are likely to be very ill, possibly beyond all help; and they are also the patients most likely to succumb in the first twenty-four hours before any treatment can be effective. A study of the mortality reports in the literature of the past few years

TABLE III

COMPARISON OF METHODS IN TREATMENT OF CORONARY ARTERY THROMBOSIS

YEAR	ATTACKS	DEATHS	MORTALITY RATE (%)	MORTALITY EXCLUSIVE 1ST 24 HR. (%)	MORTALITY 1ST ATTACK (%)
1930-32*	131	52	39.7	33.6	36
1933-34†	111	45	40.5	33.0	37
1934-36‡	145	30	20.7	16.0	10

\*Regular diet. Digitalis and nitroglycerin.

†Regular diet only. (1933 to May, 1934)

‡Undernutrition only. (May, 1934, to 1936)

(Table IV) indicates that these rates are much higher than those in our series treated with low calorie diets. The mortality rate of American and foreign authors for all attacks ranged from 38 to 53 per cent, whereas ours was 16.5 per cent; and for the first attack only, their rates were 24 to 35 per cent as against 8 per cent in our cases. We believe that this difference cannot be explained, except perhaps in very small part, on the basis of recognition of mild cases through better diagnostic acumen. For although we have included such cases, we have also included severely ill patients hitherto classified as suffering from congestive heart failure, auricular fibrillation, and peripheral shock. Furthermore, the statistics quoted for comparison cover the years immediately preceding our test period, and it is probable that in both instances the same criteria were used for the diagnosis of coronary thrombosis.

Clinical observation also has emphasized the value of the low calorie diet. In the great majority of cases pain disappeared after the first two days of this diet. If a regular diet was resumed too soon, pain

\*It should be noted that in 1930 and 1931, digitalis and nitroglycerin were used not infrequently, yet the mortality rates in these years were approximately the same as those for 1932 and 1933 when the use of these drugs had been discontinued.



TABLE IV  
MORTALITY RATE AND METHOD OF TREATMENT FOR CORONARY ARTERY THROMBOSIS BY DIFFERENT AUTHORS\*

	PARKINSON & BEDFORD 1928	LEVINE 1929	CONNER & HOLT 1930	COOMBS 1932	CLARK 1933	PADILLA & COSSIO 1934	HOWARD 1934	COOKSEY 1935	JERVELL 1935	MASTER, JAFFE & DACK 1936
No. cases	100	143	287	144	19	92	165	53	65	267
Mortality			24%			27-35%	24.2%			8%
1st attack	32%			34%						
Exclusive										
sudden										
death										
All attacks		53%			47.6%	38%		39.6%	47.7%	16.5%
<i>Treatment</i>										
Nitroglycerin	0	0					Fibrillation			0
Digitalis	+	+					0			0
Adrenalin		Early shock								0
Quinidine		Vent. tachy- cardia								
Rest	+	+					+	+		0
Morphine	+	+					+			+
Oxygen		+					+			+
Diet		Soft solid					High carbo- hydrate			+
										800 cal.

\*Blank spaces indicate no mention by author; 0 signifies treatment considered contraindicated.

often recurred. Patients learned that small meals were most agreeable and occasionally difficulty was experienced in persuading them to eat more food. Foods like fruit juices and milk and cream, which the patient could not ordinarily tolerate, were easily taken when the low calorie diet was instituted. In the stage of shock it is obvious that forcing food may not only produce symptoms but actually may be dangerous to the patient. It is only logical to give small quantities of food such as 300 to 700 calories a day, as the whole organism requires complete rest.

The close relationship between cardiac function and ingestion of food has been commented upon frequently. Heberden<sup>38</sup> in 1768 noted that his patients developed an anginal syndrome after meals. Karrel<sup>39</sup> reported the value of a low calorie milk diet. Roemheld<sup>40, 41</sup> has written in detail of the gastroduodenal syndrome and believes that distention of the stomach caused by a heavy meal interferes with the action of the heart. He found that distending the stomach produced an anginal syndrome, extrasystoles, tachycardia, faintness, belching, etc. Using the x-ray, Levyn and Rose<sup>42</sup> arrived at similar conclusions. In experiments on animals, extrasystoles, auricular flutter, auricular fibrillation, etc., have been produced by manipulation of the abdominal viscera.<sup>43, 44, 45</sup>

*Food and Cardiac Output.*—Another explanation of the beneficial influence of diminished food ingestion on the heart lies in the resulting decrease in metabolism with its accompanying decrease in cardiac output. Grollman<sup>22</sup> and Kisch and Schwarz<sup>46</sup> and Jarisch and Liljestrand<sup>47</sup> and, more recently, Gladstone<sup>48</sup> have demonstrated a rise in cardiac output following a meal. Wayne and Graybiel<sup>49</sup> in their clinical study of angina pectoris reasoned that the pain brought on by a meal was due to the added strain on the heart. These authors and also Master<sup>50</sup> found that exercise tolerance was reduced after a meal.

Additional evidence of the effect of food restriction on the body metabolism is provided by the work of Soderstrom, Barr and DuBois,<sup>51</sup> who showed that small meals when frequently taken produce less specific dynamic action than the same food divided into three meals. McCann<sup>52</sup> and Richardson and Mason<sup>53</sup> showed that following starvation the specific dynamic action of food is less than when following a regular diet. In a diet of 800 calories both these factors are in play.

The value of low calorie diets in patients with coronary thrombosis is thus confirmed by experimental and clinical observations. A patient at complete rest requires less food and less food intake makes correspondingly smaller demands on the heart muscle.

*Effect of Undernutrition on the Circulation.*—In previous articles<sup>24-27</sup> we have reported the effect of undernutrition on the basal metabolism and the circulation of patients suffering from coronary artery disease. In forty-two patients it was shown that the basal metabolic rate could be

lowered to -20 to -35 per cent and that, by varying the amount of food, the patient could be maintained at definite levels of basal metabolism. To attain the drop in basal metabolic rate to -20 to -30, a loss of at least 6 per cent of the initial body weight was necessary. This loss of weight appeared harmless. Indeed, to a patient who is overweight, it is valuable, for in the overweight the domes of the diaphragm are elevated and the vital capacity is diminished. Exercise tolerance is definitely reduced and studies in circulatory dynamics show that the obese patient is handicapped.<sup>54</sup>

*Low Calorie Diet and Work of Heart.*—The postulate that a lowered basal metabolic rate has a favorable effect on the heart is not novel. In 1900 Hirschfeld<sup>55</sup> concluded that undernutrition lightened the work of the heart. Lusk<sup>56, 57</sup> was aware of the beneficial influence of a low basal metabolic rate upon the cardiovascular system. DuBois<sup>58</sup> very recently expressed the hope that a drug capable of depressing metabolism would be introduced in the treatment of heart disease. A low calorie diet may satisfy this need.

The effect of the low calorie diet on the heart and circulation has been specifically investigated in our previous studies<sup>34-37</sup> (Table V). It was shown that the pulse rate in our patients fell to 50-60 beats per minute and occasionally below 45. After the pulse and blood pressure readings had remained constant for several weeks, an increase in the diet produced a definite rise in pulse rate. The systolic, diastolic, and pulse pressures were also raised. Benedict and his coworkers<sup>59</sup> and also Rubner<sup>60</sup> reported similar effects on blood pressure and pulse in normal subjects. Since the work of the heart is dependent upon the blood pressure and pulse rate,<sup>61, 62</sup> it is evident that undernutrition by lowering basal metabolism decreases the work of the heart.

Slowing of the pulse rate not only lessens the work of the heart but has been shown experimentally to be most efficient for the heart since less oxygen per unit of time is required for a given amount of work.<sup>63-65</sup>

That a reduction in basal metabolism diminishes the work of the heart was shown directly by Altschule,<sup>66</sup> who measured the cardiac output following total thyroidectomy. He found that a drop in basal metabolic rate of 30 per cent effected a reduction of 40 per cent in the work of the heart. A similar study<sup>67</sup> was made by Dack in one of our patients in whom the cardiac output measured 2.76 liters per minute (Table V) after the basal metabolic rate had dropped to -30 per cent. On an increased diet, the basal metabolic rate rose to -5 per cent and the cardiac output to 4.15 liters. The pulse rate which had averaged 58 on the low diet rose to 71; the systolic blood pressure rose from 96 to 128 mm.; and the diastolic from 65 to 86 mm. Hg. From these observations it was calculated that there was a reduction of 49 per cent in the work of the heart during the low calorie intake.

TABLE V

INFLUENCE OF UNDERNUTRITION ON CARDIAC OUTPUT AND WORK OF HEART  
(H. F., MALE, AGED 40)

DIET CALORIES	B. M. R. PER CENT	PULSE RATE	BLOOD PRESSURE		CARDIAC OUTPUT LITERS/MIN.	CARDIAC WORK KG. M./MIN.
			SYSTOLIC	DIASTOLIC		
800	-30	58	96	65	2.76	3.0
2,000	-5	71	128	86	4.15	5.9
Change	-25%	-18%	-25%	-24%	-32%	-49%

*No Loss of Cardiac Efficiency in Undernutrition.*—The reduction in cardiac output during undernutrition is not associated with diminished cardiac efficiency. This was shown by Benedict and his associates<sup>59</sup> and by Chittenden<sup>68</sup> and Jaffe, Poulton and Ryffel,<sup>69</sup> who studied the response of their patients to exercise. Despite a continued low basal metabolic rate, our patients, too, showed no diminution in vital capacity, exercise tolerance, or blood velocity and were able to return to moderate activity while still undernourished. Pain was minimal. These observations on metabolism and circulatory dynamics in our patients indicate that the low calorie diet is beneficial to the heart.

*Possible Ill-Effects of Diet.*—No ill-effects were noted during prolonged underfeeding. The blood sugar, blood protein, and blood cholesterol remained normal. Lusk<sup>56, 57</sup> and Rubner<sup>60</sup> have shown that loss of body protein is very slight on a diet similar to ours. Acetone was never found in the urine, and no evidence of dehydration or myxedema was observed. The general good health of the patient was maintained even after months on the 800 calorie diet; indeed, the patients felt so well that it was often difficult to persuade them to increase their food intake.

#### SUMMARY

1. Two hundred and forty-three patients suffering from coronary artery thrombosis were treated by a low calorie diet and prolonged rest in bed. Digitalis, adrenalin, or nitrites were not used.

2. The mortality rate in 267 attacks was 16.5 per cent; in first attacks only 8 per cent. Most patients survive an initial attack of coronary thrombosis. Almost one-half of our patients had suffered one or more previous attacks.

3. Coronary thrombosis is not uncommon in women. The ratio of men to women was 3 to 1. It occurs not infrequently in the fourth and fifth decades and the prognosis in these is better than in the older age groups. The average age in our series was fifty-four years.

4. Hypertension, which preceded the attack in 66 per cent of cases, did not directly influence the prognosis. When coronary thrombosis occurs in women, hypertension or diabetes is usually present.

5. Infarction of the anterior and posterior surface of the left ventricle occurs with equal frequency; there is no difference in prognosis.

6. Irregularities of the heart developing during an attack were transitory in most cases and required no specific treatment.

7. Evidence is given that the good results reported in this series may be attributed in part to the undernutrition therapy which eliminates gastrocardiac reflexes, minimizes the rise in metabolism and cardiac output which usually follows a meal, and gradually lowers the basal metabolic rate. This effects a decrease in pulse rate and blood pressure, and so a diminution in the work of the heart.

8. No ill effects were observed following the use of the low calorie diet.

9. Instances of coronary artery thrombosis occur which are inevitably fatal because of the size of one or several simultaneous infarctions or because of the severe degree of involvement of all the coronary vessels. From this series of cases, however, it appears that in the main the prognosis of an attack is hopeful and, indeed, death in the first attack is infrequent.

#### REFERENCES

1. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* 1: 4, 1928.
2. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* 8: 245, 1929.
3. Conner, L. A., and Holt, Evelyn: The Subsequent Course and Prognosis in Coronary Thrombosis. An Analysis of 287 Cases, *AM. HEART J.* 5: 705, 1930.
4. Coombs, C. F.: Prognosis in Coronary Thrombosis, *Bristol Med.-Chir. J.* 49: 277, 1932.
5. Clark, L. J.: Prognosis in Coronary Disease, *New Orleans M. & S. J.* 86: 365, 1933.
6. Padilla, T., and Cossio, B.: Prognosis in Myocardial Infarcts, *Rev. argent. de cardiol.* 1: 181, 1934.
7. Howard, T.: Coronary Occlusion: Based on the Study of 165 Cases, *M. Times & Long Island M. J.* 62: 337, 1934.
8. Cooksey, W. R.: Coronary Thrombosis: Follow-Up Studies With Especial Reference to Prognosis, *J. A. M. A.* 104: 2063, 1935.
9. Jervell, A.: Elektrokardiographische Befunde bei Herzinfarkt, *Acta med. Scandinav. Supplement* 68, 1935.
10. Dublin, L. I.: The Problem of Heart Disease, *Harper's Monthly Magazine* 154: 196, 1927.
11. David, N. A.: Dilaudid and Morphine Effects on Basal Metabolism and Other Body Functions, *J. A. M. A.* 103: 474, 1934.
12. Eppinger, H., Von Popp, L., Schwarz, A.: *Ueber des Asthma Kardiale*, Berlin, 1924, Julius Springer.
13. Fraser, F. R.: Cardiac Dyspnea, *Lancet* 1: 643, 1927.
14. Harrison, T. R.: *Failure of the Circulation*, Baltimore, 1935, The Williams and Wilkins Co., pp. 171, 182, 297.
15. Fenn, G. K., and Gilbert, N. C.: Anginal Pain as a Result of Digitalis Administration, *J. A. M. A.* 98: 99, 1932.
16. Bellet, S., Johnston, C. C., and Schechter, A. B.: Effect of Cardiac Infarction on the Tolerance of Dogs to Digitalis: An Experimental Study, *Arch. Int. Med.* 54: 509, 1934.
17. Hadfield, G.: Cardiac Infarction, *Lancet* 1: 189, 1928.
18. Hubble, D.: Angina Pectoris and Coronary Disease, *Lancet* 1: 908, 1930.
19. Luten, D.: Contributing Factors in Coronary Occlusion, *AM. HEART J.* 7: 36, 1931.
20. Prodger, S. H., and Ayman, D.: Harmful Effects of Nitroglycerine With Special Reference to Coronary Thrombosis, *Am. J. M. Sc.* 184: 480, 1932.
21. Sprague, H. B., and White, P. D.: Nitroglycerine Collapse: A Potential Danger in Therapy. Report of Three Cases, *M. Clin. North America* 16: 895, 1933.
22. Grollman, A.: *The Cardiac Output of Man in Health and Disease*, Baltimore, 1932, Charles G. Thomas, pp. 178, 183, 189.

23. Riesman, D., and Harris, S. E.: Disease of the Coronary Arteries With a Consideration of the Data on the Increasing Mortality of Heart Disease, *Am. J. M. Sc.* 187: 1, 1934.
24. Levine, S. A., Ernestone, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina, *Arch. Int. Med.* 45: 191, 1930.
25. Cottrell, J. E., and Wood, F. C.: The Effect of Epinephrin in Angina Pectoris With Report of a Case, *Am. J. M. Sc.* 181: 36, 1931.
26. Bedford, D. E.: Prognosis in Coronary Thrombosis, *Lancet* 1: 223, 1935.
27. Sutton, D. C., and Davis, M. D.: Effects of Exercise on Experimental Cardiac Infarction, *Arch. Int. Med.* 48: 1118, 1931.
28. Moritz, A. R., and Beck, C. S.: The Production of a Collateral Circulation to the Heart, *AM. HEART J.* 10: 874, 1935.
29. Barnes, A. R., and Wade, J. L.: Acute Coronary Occlusion: Clinical Electrocardiographic and Necropsy Findings in Two Cases, *M. Clin. North America* 19: 499, 1935.
30. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and Resulting Myocardial Changes, *AM. HEART J.* 10: 567, 762, 1935.
31. Smith, F. M., Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, *J. A. M. A.* 105: 2, 1935.
32. Wilson, F. N., Barker, P. S., MacLeod, A. G., and Klostermeyer, L. I.: The Electrocardiogram in Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* 29: 1006, 1932.
33. Wolferth, C. C., Wood, F. C., and Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle: Electrocardiographic Characteristics, *Arch. Int. Med.* 56: 77, 1935.
34. Master, A. M., Jaffe, H. L., and Dack, S.: Low Basal Metabolic Rates Obtained by Low Calorie Diets in Coronary Artery Disease, *Proc. Soc. Exper. Biol. & Med.* 32: 779, 1935.
35. Master, A. M., Jaffe, H. L., and Dack, S.: The Basal Metabolic Rate in a Patient With Coronary Artery Thrombosis When Placed on an 800 Calorie Diet, *J. Mt. Sinai Hosp.* 1: 263, 1935.
36. Master, A. M.: Coronary Artery Thrombosis With Treatment by Prolonged Rest in Bed and Low Calorie Diet: Improved Prognosis, *J. A. M. A.* 105: 337, 1935.
37. Master, A. M., Jaffe, H. L., and Dack, S.: Undernutrition in the Treatment of Coronary Artery Disease (Particularly Thrombosis): Studies on Basal Metabolism and Circulation, *J. Clin. Investigation* 15: 353, 1936.
38. Heberden, W.: Some Account of a Disorder of the Breast, *Med. Trans. (College of Physicians) London* 2: 59, 1786.
39. Karrel, P.: De la Cure de Lait, *Arch. gén. de Méd.* 118: 513, 1866.
40. Roemheld, L.: Treatment of "Gastro-Cardiac Syndrome" (Gastric Cardiopathy), *Am. J. M. Sc.* 182: 13, 1931.
41. Roemheld, L.: Der Gastro-Kardiale Symptomenkomplex, eine besondere Form sogenanter Herzneurose, *Ztschr. f. phys. u. diätet. Therap.* 16: 339, 1912.
42. Levyn, L., and Rose, W. J.: Viscero-cardiac Reflexes, *Radiology* 22: 622, 1934.
43. Owen, S. E.: A Study of Viscerocardiac Reflexes: 1. The Experimental Production of Cardiac Irregularities by Visceral Stimulation, *AM. HEART J.* 8: 496, 1933.
44. Hinrichsen, Josephine, and Ivy, A. C.: Effect of Stimulation of Visceral Nerves on Coronary Flow in Dogs, *Arch. Int. Med.* 51: 932, 1933.
45. Crittenden, P. J., and Ivy, A. C.: Study of Viscerocardiac Reflexes: The Experimental Production of Cardiac Irregularities in Icteric Dogs With an Analysis of the Role Played by Nausea and Vomiting, *AM. HEART J.* 8: 507, 1933.
46. Kisch, B., and Schwarz, H.: Das Herzschlagvolumen und die Methodik seiner Bestimmung, *Ergebn. d. inn. Med. u. Kinderh.* 27: 169, 1925.
47. Jarisch, A., and Liljestrang, C.: Ueber des Verhalten des Kreislaufs bei Muskelarbeit nach dem Essen und bei Flüssigkeitszufuhr, *Skandinav. Arch. f. Physiol.* 51: 235, 1927.
48. Gladstone, S. A.: Cardiac Output and Related Functions Under Basal and Post-Prandial Conditions: A Clinical Study, *Arch. Int. Med.* 55: 533, 1935.
49. Wayne, E. J., and Graybiel, A.: Observations on the Effect of Food, Gastric Distention, External Temperature and Repeated Exercise on Angina of Effort With a Note on Angina Sine Dolore, *Clin. Sc.* 1: 287, 1934.
50. Master, A. M.: The Two-Step Test of Myocardial Function, *AM. HEART J.* 10: 495, 1935.

51. Soderstrom, G. F., Barr, D. P., and DuBois, E. F.: The Effect of a Small Breakfast on Heat Production, *Arch. Int. Med.* 21: 613, 1918.
52. McCann, W. S.: An Observation of the Effect of a Protein Meal Given to a Man at the End of an Eight Day Fast, *Proc. Soc. Exper. Biol. & Med.* 17: 173, 1920.
53. Richardson, H. B., and Mason, E. H.: The Effect of Fasting in Diabetes as Compared With a Diet Designed to Replace the Foodstuffs Oxidized During a Fast, *J. Biol. Chem.* 57: 587, 1923.
54. Master, A. M., and Oppenheimer, Enid T.: A Study of Obesity; Circulatory, Roentgen-Ray and Electrocardiographic Investigations, *J. A. M. A.* 92: 1652, 1929.
55. Hirschfeld, F.: Die Anwendung der Ueberernahrung und der Unterernahrung, Frankfurt, a/M., 1897, T. Rosenheim, p. 63; *Nahrungsmittel und Ernahrung des Gesunden und Kranken*, Berlin, 1900, A. Hirschwald, p. 199.
56. Lusk, G.: The Physiological Effect of Undernutrition, *Physiol. Rev.* 1: 522, 1921.
57. Lusk, G.: The Science of Nutrition, ed. 4, Philadelphia, 1928, W. B. Saunders Co., p. 173.
58. DuBois, E. F.: Total Energy Exchange in Relation to Clinical Medicine, *Bull. New York Acad. Med.* 9: 680, 1933.
59. Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, *Carnegie Inst. of Washington Publication No. 280*, 1919.
60. Rubner, M.: Die Physiologische Bedeutung des Stickstoffs, *Verhandlungen d. ges. deutscher Naturforscher u. Arzte* 86: 81, 1921.
61. Erlanger, J., and Hooker, D. R.: An Experimental Study of Blood Pressure and Pulse Pressure in Man, *Johns Hopkins Hosp. Report* 12: 145, 1904.
62. Rosen, I. T., and White, H. L.: The Relation of Pulse Pressure to Stroke Volume, *Am. J. Physiol.* 76: 168, 1926.
63. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, *J. Physiol.* 62: 243, 1926, 1927.
64. Hemingway, A., and Fee, A. R.: Relationship Between the Volume of the Heart and Its Oxygen Usage, *J. Physiol.* 63: 299, 1927.
65. Harrison, T. R.: See ref. 14, p. 90.
66. Altschule, M. D.: The Cardiac Output and the Work of the Heart in Hypothyroidism, *J. Clin. Investigation* 14: 700, 1935.
67. Dack, S.: The Effect of Undernutrition on the Minute Volume Output and Work of the Heart in a Case of Coronary Thrombosis, *J. Mt. Sinai Hosp.* 3: 74, 1936.
68. Chittenden, R. H.: Physiological Economy in Nutrition, *The Popular Science Monthly* 63: 123, 1903.
69. Jaffe, J., Poulton, E. P., and Ryffel, J. H.: The Respiratory Metabolism in a Case of Prolonged Undernutrition, *Quart. J. Med.* 12: 334, 1918.

## A STUDY OF THE CARDIAC OUTLINE\*

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THE practice of cardiac radioscopy is based on our knowledge of the relative positions of the chambers of the heart and the conception that each chamber may be rendered border-forming by rotating the patient into suitable positions. The relative length of each segment of the cardiac silhouette and its degree of curvature offer valuable information concerning the size and depth of the outlined chamber.

Emphasis has been placed recently on cardiac enlargement as a prognostic sign in heart disease.<sup>1</sup> Increase in the size of a single chamber

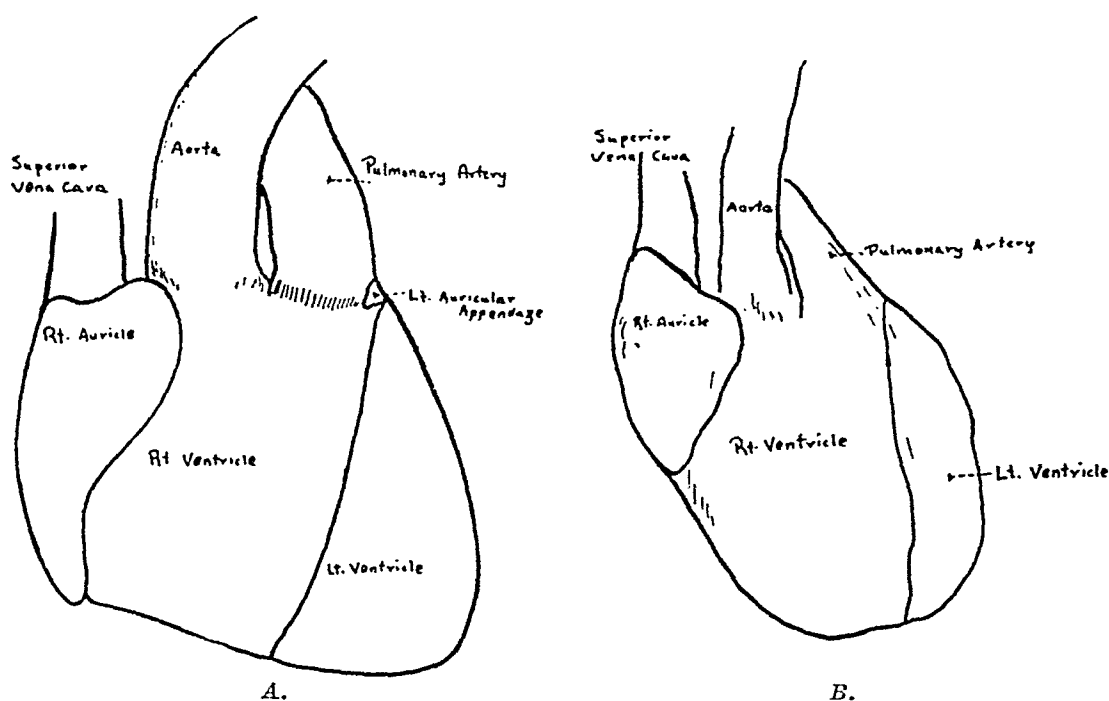


Fig. 1.—A, outline of normal heart in situ. B, outline of the same heart removal from the thorax.

is of the greatest importance. Recent interest in the radiological appearance of individual chamber enlargement and the position and configuration of the great vessels has prompted this study.<sup>2</sup>

Post-mortem examinations of the heart in situ were made in twenty-eight cases. The trachea was clamped before the sternum was removed in the first six cases in an effort to keep the lungs relatively inflated. Subsequent observations showed that this precaution was unnecessary since minor displacements of the lungs did not affect the position of the heart appreciably. Manipulation of the diaphragm, preexisting

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hydrothorax, or pleural adhesions of minor degree did not alter the cardiac configuration or position. Pleuropericardial adhesions likewise did not influence the situation of the cardiac borders, in the absence of intrapericardial adhesions, unless they were extensive.

After the sternum was removed, the pericardium was opened widely. An accurate sketch of the heart in situ was made. The size and exact positions of the various cardiac segments and great vessels were noted. Despite the facts that films taken during life were taken in the erect position at a 2-meter distance and the post-mortem measurements were made with the body in the supine position, the measurements were in fair agreement. But the difference in the configuration of the heart

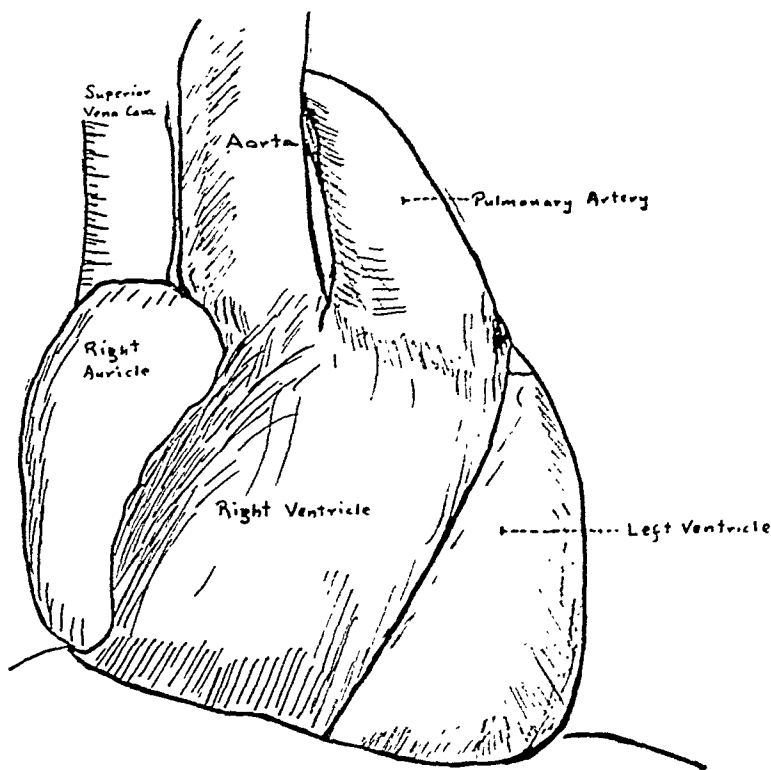


Fig. 2.—I. E., male, aged thirty-seven years. Bilateral tuberculosis. The left auricular appendage appears as a small triangular area at the junction of the pulmonary artery and left ventricle.

borders and their relative positions before and after removal of the organ from the body were particularly striking (Fig. 1).

It is understood that the correlation offered by this study is approximate at best. We cannot take into account the effect of the rotation of the heart during systole or the results of the relaxation of the cardiac musculature during diastole. It is doubtful, however, whether these factors are of clinical significance.

The left border of the normal heart is formed by three main arcs. These consist of the arch and upper thoracic portion of the aorta, the pulmonary artery, and the left ventricle. An elongated left auricular

appendage is sometimes seen extending from between the two left pulmonary veins to a position near the junction of the pulmonary artery and the left ventricle. This may form a small portion of the border, but is insignificant for all practical purposes (Fig. 2).

A small portion of the pulmonary conus is sometimes seen on the left cardiac border in the more hypoplastic type of heart (Fig. 3). The second left arc in these individuals consists of two portions, the pulmonary artery lying above the conus. The pulmonary artery is always the longer of the two segments. The left auricular appendage may extend from behind to overlap partially the conus, thereby increasing the apparent convexity of the arc.

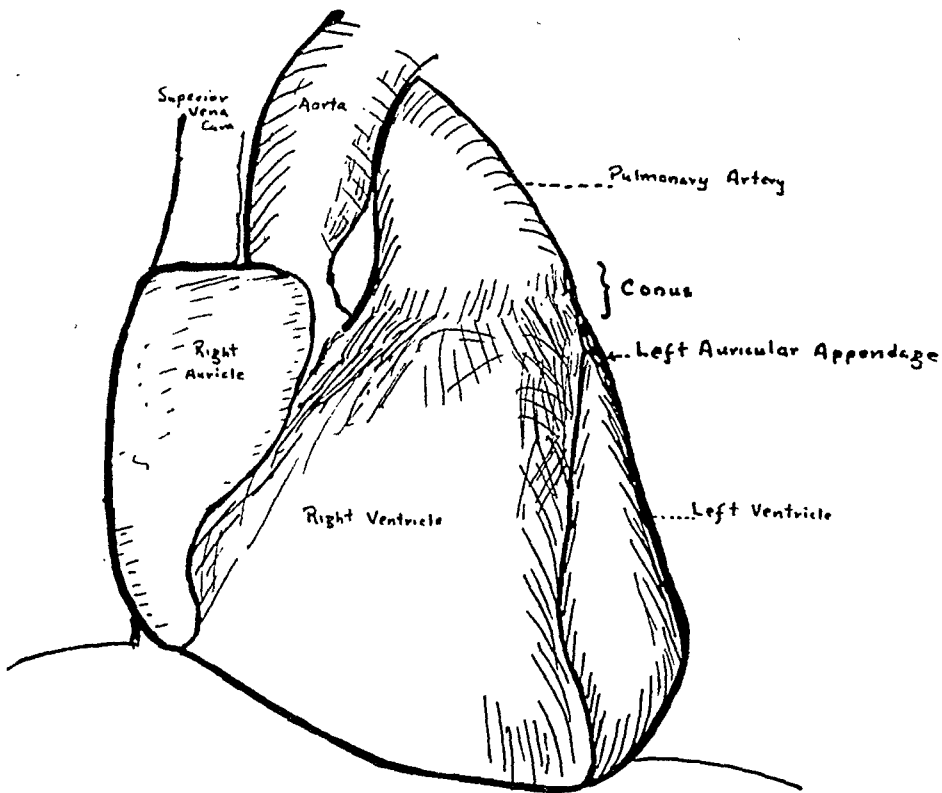


Fig. 3.—E. G., female, aged thirty-five years. Brain tumor. The pulmonary conus is border-forming on the lowermost part of the second left arc, immediately above the left auricular appendage.

The right border of the normal heart is formed entirely by the lateral border of the right auricle (Figs. 2 and 3). The right auricular appendage is situated anterolaterally and occupies the upper two-thirds of the right border. It is a wide chamber in free communication with the body of the auricle, and may extend as far anteriorly as the mid-line of the heart. The lower one-third of the right auricle lies more posterolaterally and varies considerably in its transverse diameter. At times it measures but 1 cm. across. One cannot estimate the transverse extension of this chamber in the postero-anterior projection because its mesial border is lost against the dense shadow of the remainder of the heart.

The superior vena cava is frequently visualized arising from the upper part of the right border. Infrequently one may demonstrate the supradiaphragmatic portion of the inferior vena cava.

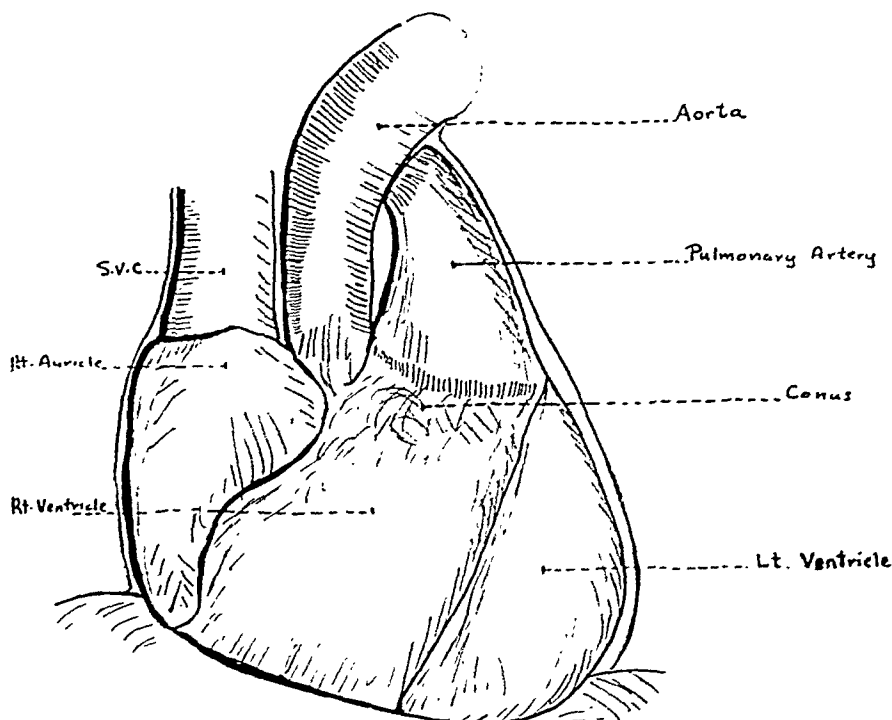


Fig. 4.—C. B., female, aged twenty-seven years. Advanced bilateral tuberculosis. The pulmonary artery of the drop type of heart courses parallel to the aorta for an appreciable distance.

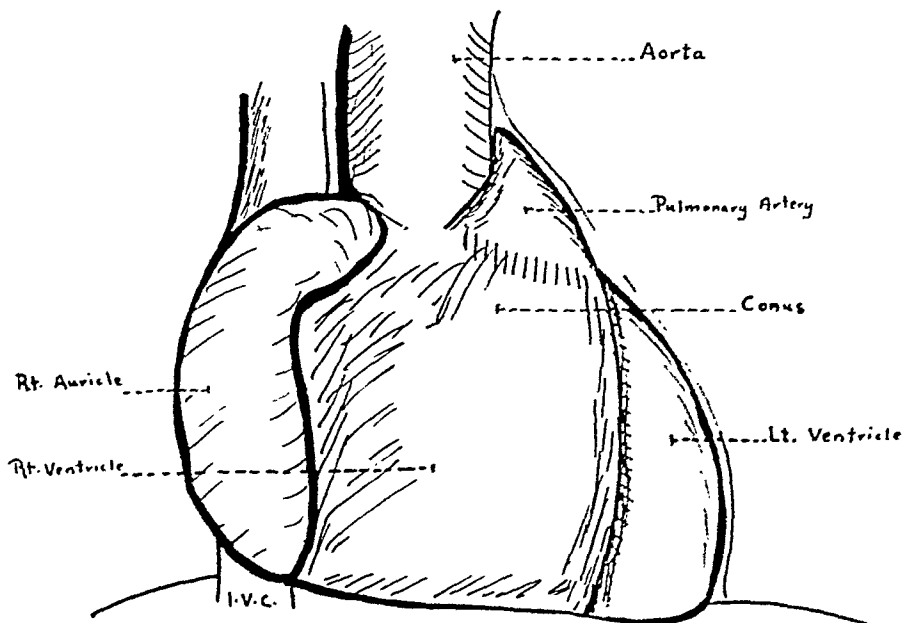


Fig. 5.—C. R., male, aged sixty-five years. Carcinoma of the larynx. The pulmonary artery of the transverse type of heart approximates the aorta for only a short distance.

The diaphragmatic surface of the heart is formed in most part by the right ventricle. The inferior vena cava and, to a more appreciable

extent, the apex of the left ventricle form the outermost portions of the diaphragmatic area.

The body of the left auricle is never border-forming in the frontal projection of normal hearts. It may be seen occasionally as a circular or oval shadow of slightly increased density in the center of the cardiac silhouette. Dilatation of the left auricle may cause its right border to project beyond the shadow of the right auricle. Displacement of its left lateral border beyond the shadow of the second and third left cardiac segments is very unusual, even in the presence of excessive

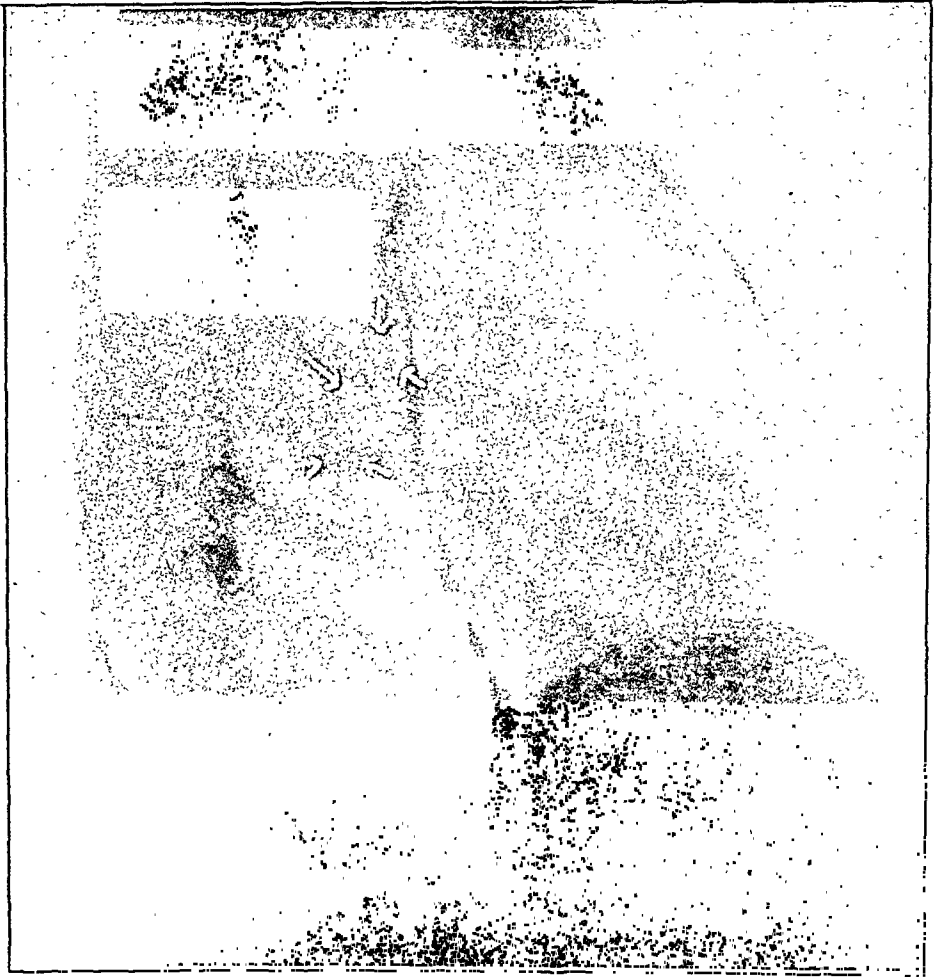


Fig. 6.—The pulmonary artery is well outlined in the left oblique position. The aortic impression against the barium filled esophagus is seen just above the pulmonary artery.

auricular dilatation. I have been able to find but one such case in the literature.<sup>3</sup> Another is reported at the end of this paper.

The left auricular appendage is rarely dilated appreciably. This may be ascribed to its dense structure and its comparative isolation from the body of the auricle.

The angle of origin of the main stem of the pulmonary artery from the conus or outflow portion of the right ventricle is of interest. The artery arises almost perpendicularly from the conus in the normal "drop" type of heart, courses parallel to the aorta for as much as

from 5 to 7 cm. before it spirals around the aorta and divides into the right and left pulmonary arteries. Its origin in the more transverse type of heart is more oblique and, as a rule, the main stem is shorter (Figs. 4 and 5). Frequently a part of the left main branch can be seen in the frontal view springing from the upper portion of the second left segment. One is able in some cases to trace almost the entire length of the left pulmonary artery by rotating the patient slowly into the left oblique position while observing the left pulmonary artery (Fig. 6).

The superior interventricular indentation is usually located at the point where the pulmonary artery swings vertically away from the

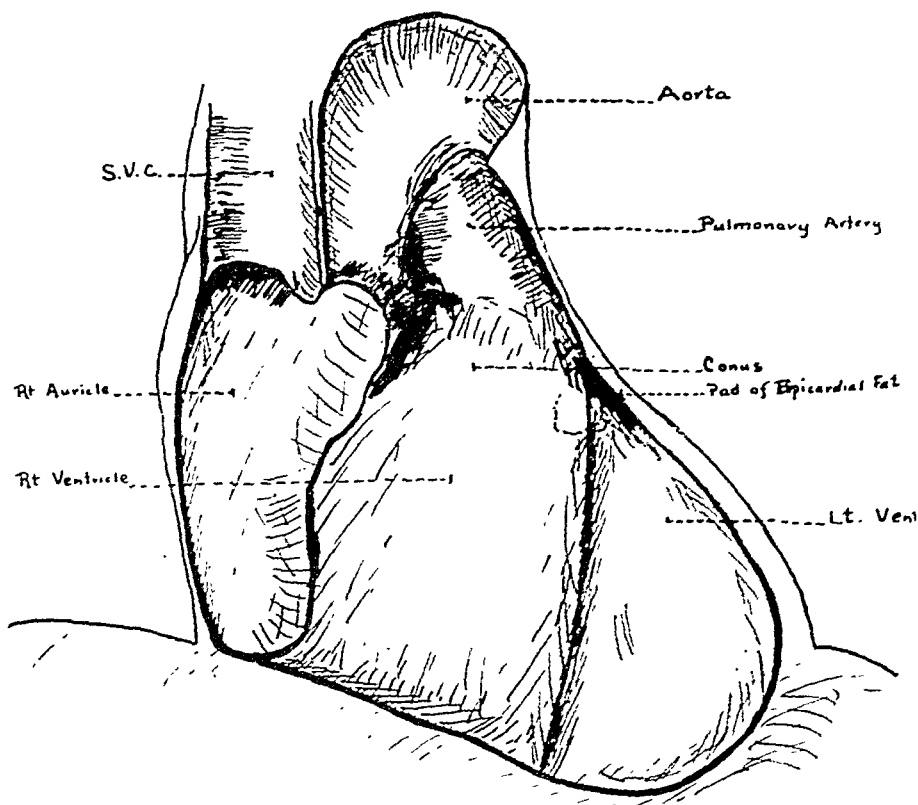


Fig. 7.—S., male, aged forty-seven years. Polycythemia vera. Heavy deposits of subepicardial fat obscures the superior interventricular indentation.

left ventricle. Its level can be approximated fluoroscopically by noting the point on the left cardiac border where the lower and middle segments pulsate forcibly in opposite directions—the so-called “oscillating point.” This can be differentiated from the twitching pulsation of the left auricular appendage when it is border-forming. A gas-filled stomach bubble often enables one to visualize the apex, and is of considerable aid in determining the true extent of the left ventricular segment. The inferior interventricular indentation can be identified in the right oblique position, and occasionally is demonstrable in the postero-anterior position through the stomach bubble.

The position of the anterior interventricular sulcus may be estimated by drawing a line between the inferior interventricular indentation to the oscillating point between the second and third left cardiac segments. In order to localize the septum, it would be necessary to localize the posterior interventricular sulcus. I know of no method for doing this, since any rotation of the heart changes the posterior sulcus' position. Even if one could accurately localize both sulci, it would be extremely difficult to determine whether and how far the interventricular septum bulges into the right ventricle.

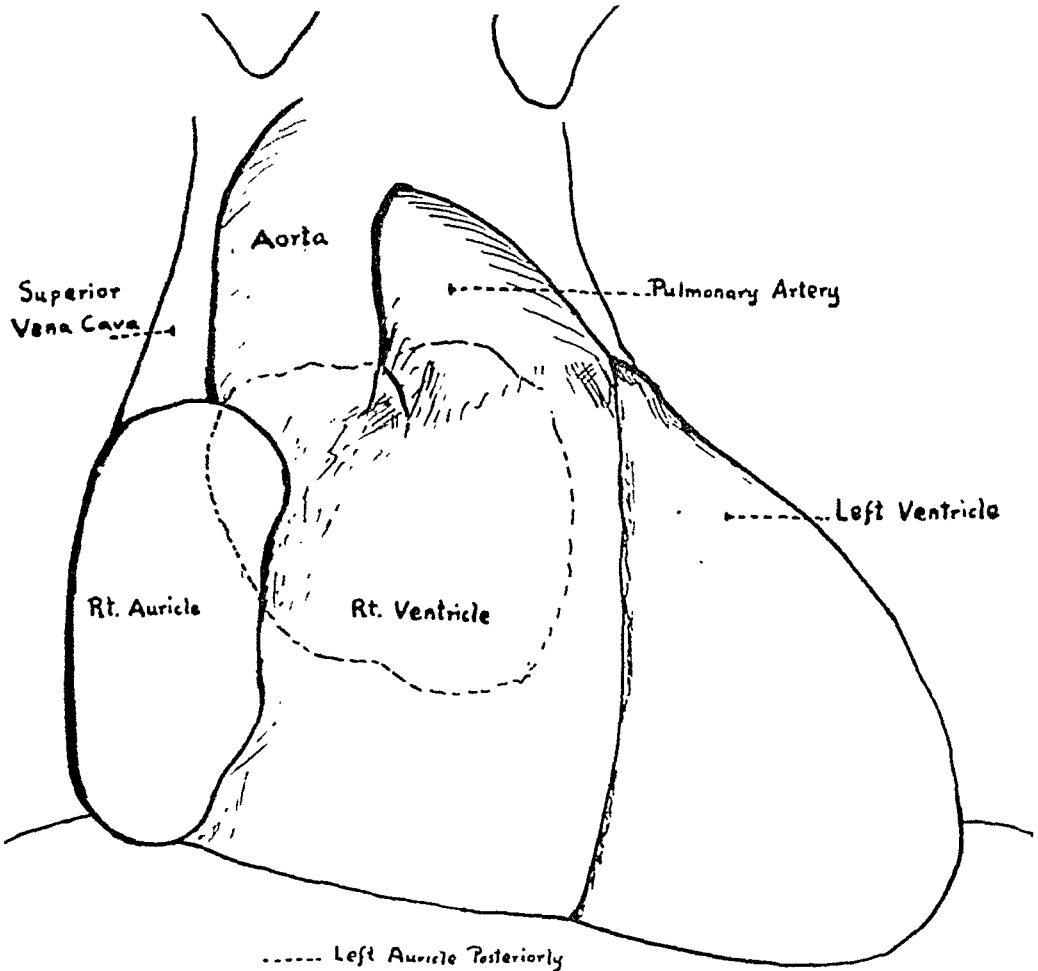


Fig. 8.—L. N., male, aged forty-one years. Uremia. The left auricle is deviated to the right because of the clockwise rotation of the heart produced by the enlarged left ventricle.

When the heart is seen in situ with the pericardium open, each segment is clearly outlined. As seen on the radiogram, the borders are usually smooth. It has been suggested that this may be due to the shadow cast by the pericardial sac. Heavy deposits of subepicardial fat (Fig. 6\*), or thick pericardial adhesions may also obscure normal separating points. Pericardial effusions of appreciable degree completely obliterate all landmarks.

\*The film for Fig. 6 is reproduced through the courtesy of Dr. M. G. Wasch of the Jewish Hospital of Brooklyn.

The characteristic findings of chamber enlargement have been adequately described in the literature.<sup>4</sup> Each chamber except the right auricle enlarges in a characteristic fashion.

During the course of this study several instances were noted in which massive enlargement of the left ventricle rotated the heart clockwise, thereby displacing the left auricle toward the right. In these instances the esophagus was deviated slightly to the right (Fig. 8), but there was no elevation of the left main bronchus.

#### CASE REPORT (FIG. 9)

R. O., a twenty-two-year-old girl was admitted with complaints of shortness of breath and palpitation. She had had rheumatic polyarthritis with cardiac in-

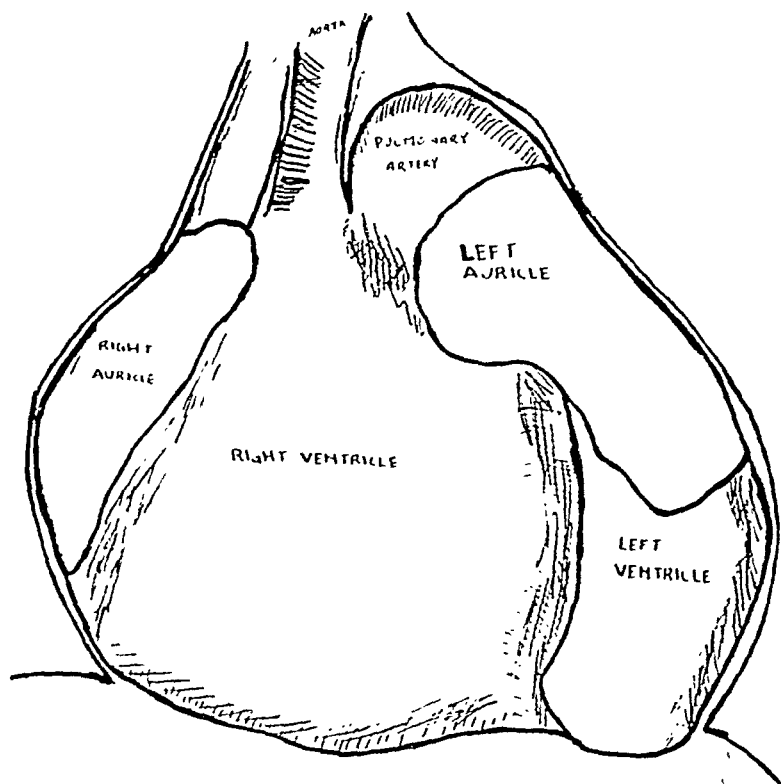


Fig. 9.—R. O'N., female, aged twenty-two years. Chronic rheumatic cardiovalvular disease with mitral stenosis. The left auricle forms approximately half of the left border. Note that the enlarged right ventricle has rotated and elevated the right auricle.

volvement at the age of five years, followed by an episode of chorea lasting several weeks at the age of eight years. Patient first noted dyspnea, palpitation and pretibial edema at the age of twenty years.

Physical examination revealed a slim, poorly nourished girl. No cyanosis. Lungs clear. Apical impulse in the fifth interspace beyond the midclavicular line. Forceful apex beat with diastolic thrill at the apex. Presystolic and systolic apical murmurs, transmitted upward. Heart action totally irregular. Liver enlarged and tender.

*Laboratory Findings.*—Hemoglobin, 70 per cent. Saccharine circulation time, 45 seconds; other circulation time, 9.6 seconds. Sedimentation rate, 12 mm. in the first hour.

*Course.*—Liver remained enlarged despite mercurial diuretics. Patient died two months after admission.

*Report of X-ray of Chest.*—"The heart is globular in shape and shows marked enlargement of the left ventricle with a marked posterior bulge. There is marked enlargement of the outflow tract and inflow tract of the right ventricle. The left auricle is seen as a central shadow of increased density in the postero-anterior view. It is enlarged horizontally and elevates and compresses the left bronchus in the vertical position. The aorta is hypoplastic, and the heart is rotated."

*Clinical Diagnosis.*—Chronic rheumatic cardiovalvular disease, with mitral stenosis and insufficiency, auricular fibrillation, congestive heart failure.

*Post-Mortem Findings.*—Heart weighed 425 gm. Right auricle was dilated. The right ventricle was markedly dilated and hypertrophied, the dilatation involving both the inflow and outflow tracts. The left auricle was tremendously dilated. The auricular appendages were free. The left ventricle was slightly dilated. The mitral valve was stenosed, showing a calcified "fish-mouth" opening. The pulmonary artery and left main bronchus were elevated. The aort was hypoplastic.

#### SUMMARY

The cardiac borders were studied in situ in twenty-eight cases. The following points are emphasized.

1. The left auricle rarely appears on the left border. The left auricular appendage may be border-forming, but it is rarely of any significance.
2. The pulmonary artery forms the major portion of the second left cardiac arc.
3. The angle of origin of the pulmonary artery with the conus may vary considerably. The length of the second left arc varies directly with the length of the pulmonary artery. The more perpendicular variety is usually the longer.
4. Enlargement of the left ventricle may rotate the heart clockwise, thereby displacing the left auricle toward the right without dilatation of the latter chamber. In these instances deviation of the barium-filled esophagus to the right does not necessarily indicate an enlargement of the left auricle.
5. An unusual case of left auricular dilatation is presented.

#### REFERENCES

1. Lewis, Sir Thomas: *Diseases of the Heart*, New York, 1932, The Macmillan Company.
2. Bedford, D. E.: Extreme Dilatation of the Left Auricle to the Right, *AM. HEART J.* 3: 127, 1927.
- East, C. F. T.: Great Dilatation of the Left Auricle, *Lancet* 1: 1194, 1926.
- Nichols, C. F., and Ostrum, H. W.: Unusual Dilatation of the Left Auricle, *AM. HEART J.* 8: 205, 1932.
- Schott, A.: Zur Kenntnis der Hochgradigen Erweiterung des Linken Vorhofes, *Klin. Wchnschr.* 3: 1067, 1924.
- Steel, D.: Extreme Dilatation of the Left Auricle, *Am. J. Roentgenol.* 26: 66, 1931.
3. Bland, E. F., Balboni, G. M., and White, P. D.: Enormous Increase of Heart Volume With Mitral Stenosis, *J. A. M. A.* 96: 840, 1931.



4. Assman, L.: *Klinische Röntgendiagnostik der inneren Erkrankungen*, ed. 4, Leipzig, 1929, F. C. W. Vogel.
- Dietlen, H.: *Herz und Gefässe im Röntgenbild*, Leipzig, 1923, Johann Ambrosius Barth.
- Nemet, G.: *Clinical Aspects of Cardiac Roentgenography*, M. Clin. North America 15: 1383, 1932.
- Nemet, G.: *Guide to Radiologic Diagnosis in Heart Disease*,'' Heart Committee of the New York Tuberculosis and Heart Association, Inc., 1931.
- O'Kane, G. H., Andrew, F. D., and Warren, S. L.: *Standardization Study of the Heart and Great Vessels in the Left Oblique Position*, Am. J. Roentgenol. 23: 373, 1930.
- Parkinson, J., and Bedford, D. E.: *The Pulmonary Artery Impression on the Esophagus*, Lancet 221: 337, 1931.
- Parkinson, J.: *Radiology of Heart Disease*, Brit. M. J. 2: 591, 1933.
- Schwedel, J. B., and Epstein, B. S.: *A Radiologic Study of the Pulmonary Artery With Special Reference to the Main Branches*, AM. HEART J. 11: 292, 1936.
- Vaquez, H., and Bordet, E.: *Radiologie du coeur et vaisseaux de la base*, Paris, 1928, J. B. Bailliere et fils.

## A STUDY OF THE QRS COMPLEX OF LEAD III IN LEFT AXIS DEVIATION\*

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IN THE routine analysis of the electrocardiogram, one is impressed with great variations in the configuration of the conventional third lead. These variations are conspicuous in that class of tracings which show left axis deviation. This analysis has been undertaken to attempt to group those records showing left axis deviation into a number of subdivisions, chosen upon the general pattern of the QRS complex as displayed on inspection and not upon degree of axis deviation, in order to demonstrate any varying significance of these patterns in disease, and, if possible, to attach diagnostic significance to changes in the much neglected Lead III.

Four hundred thirty-one records were analyzed, representing all the tracings showing left axis deviation in 1,781 consecutive electrocardiograms of subjects on whom adequate clinical data were available. Left axis deviation occurred in 24.2 per cent of the 1,781 electrocardiograms reviewed and was considered present in those tracings which displayed the major deflection upward in Lead I and downward in Lead III. Usually  $R_2$  was smaller than  $R_1$  but in twenty-two cases  $R_2$  was greater than  $R_1$ . The inclusion of this group will be discussed later. In no case was a record with a QRS width greater than 0.10 sec. included. Bundle-branch block and defective intraventricular conduction were thus eliminated. All cases were classified clinically, upon the criteria of the American Heart Association,<sup>1</sup> into "definite," "possible," "potential" and "no heart disease" groups in a rigid and critical clinical survey. For analysis in this paper, however, the cases were divided into "definitely" and "not definitely" diseased groups, the latter including those patients in the "normal," "possible" and "potential" divisions, so as to influence favorably any conclusions which may be drawn from the analysis.

A review of the 431 records disclosed seven general patterns, as shown in Fig. 1. The frequency of their occurrence, together with the number and percentages of patients showing the presence or absence of definite clinical heart disease, is summarized in Table I.

Definite heart disease often occurs in individuals with normal electrocardiograms. In 100 consecutively studied patients with heart disease, Proger and Minnich<sup>2</sup> found 38 per cent with normal electrocardiograms.

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Only 65.4 per cent of the present series of patients with left axis deviation were proved to have definite heart disease clinically. This estimate may, however, be too low because of the conservative method of classifying patients. On the other hand, one cannot safely ascribe 65.4 per cent of the instances of left axis deviation to heart disease, for a portion of this group, as in the 34.6 per cent not diseased, would undoubtedly show left axis deviation in the absence of disease. And so it is with other electrocardiographic changes. It is not only the frequency of the occurrence of a change in diseased hearts but the infrequency of its occurrence in the normal heart that establishes its value. Since most patients on whom electrocardiograms are taken are suspected of heart abnormalities, one must use care in evaluating unusual changes in these patients.

The curve pattern shown in Fig. 1, A, represents the most frequent Lead III type seen in this series. It occurred slightly more often in those without demonstrable disease (51.6 per cent) than in those with definitely diseased hearts (48.4 per cent). Almost invariably in the ab-

TABLE I

GROUP	NUMBER OF DISEASED PATIENTS	NUMBER OF PATIENTS NOT DISEASED	TOTAL
A	77 (48.4%)	82 (51.6%)	159 (36.8%)
B	29 (72.5%)	11 (27.5%)	40 (9.2%)
C	25 (75.7%)	8 (24.3%)	33 (7.9%)
Significant Q <sub>s</sub>	22 (85.0%)	7 (15.0%)	29 (6.7%)
D	108 (71.1%)	44 (28.9%)	152 (35.2%)
Curves of Proger and Minnich	30 (93.7%)	2 (6.3%)	32 (7.4%)
E	21 (91.3%)	2 (8.7%)	23 (5.3%)
F	2 (66.7%)	1 (33.3%)	3 (0.7%)
G	8 (88.9%)	1 (11.1%)	9 (2.1%)
H	8 (66.7%)	4 (33.3%)	12 (2.8%)
Total	282 (65.4%)	149 (34.6%)	431 (100.0%)

sence of disease, and often in the presence of disease, this curve type occurred in patients of the hypersthenic habitus, usually with obesity. Inversion of P<sub>3</sub> and T<sub>3</sub> was often associated, concerning which, at present, I am reporting no analysis. Proger,<sup>2</sup> in a study of 100 obese individuals with and without heart disease of the hypertensive type, found left axis deviation as frequently, and almost to the same degree, in simple obesity as in patients with obesity, hypertension, and cardiac hypertrophy. He concluded that axis deviation in the electrocardiogram of the obese patient is of no value as an aid in the diagnosis of relative ventricular hypertrophy. My experience in this group confirms his statement. The predominance of the nondiseased group in this series is due to a great extent to the fact that hypersthenic and obese individuals were often referred for electrocardiograms because the body type with "transverse heart" leads frequently to suspected enlargement clinically.

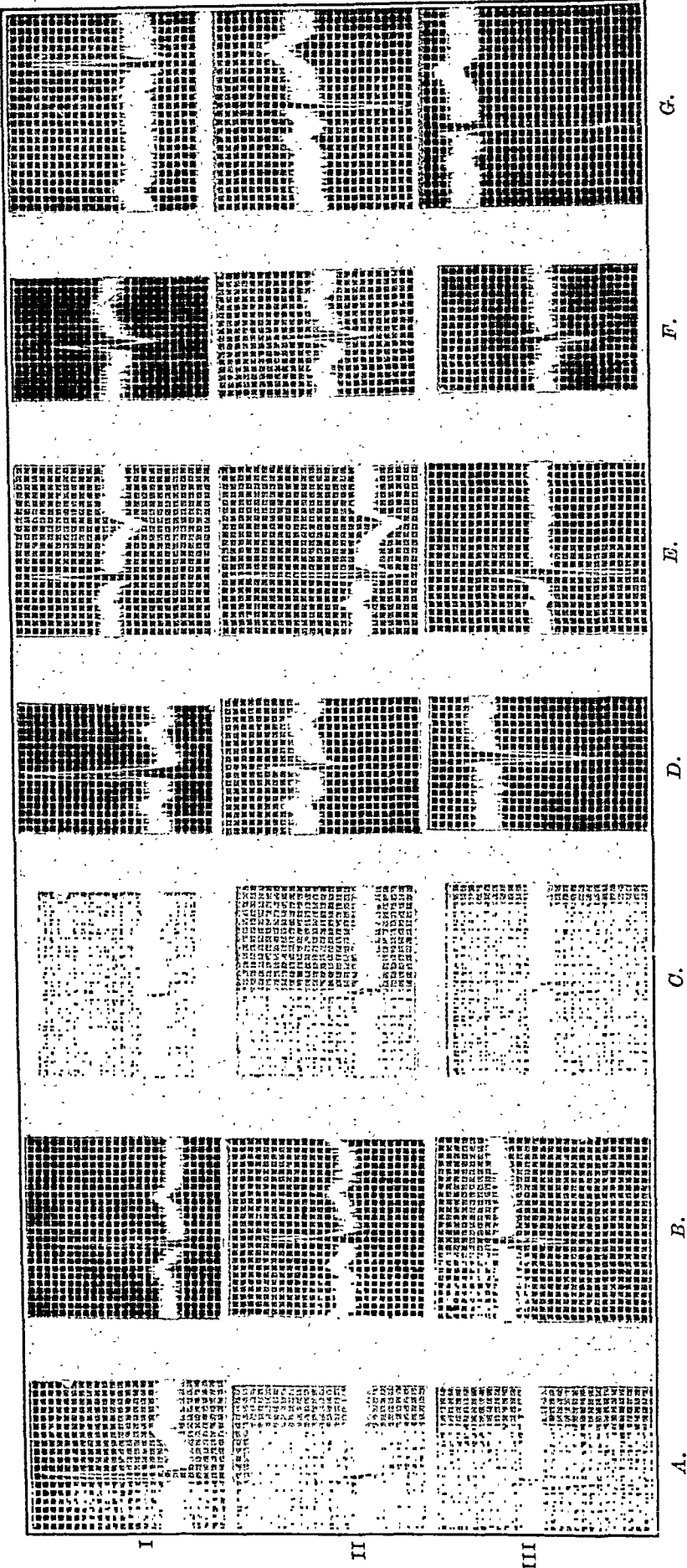


Fig. 1.—Curves illustrating Groups A to G tabulated in Table I.

Group B, as shown in Fig. 1, *B*, appears to be a variation of Group A. It represents a type of curve which may be included in a group previously described by Katz and Slater.<sup>4</sup> Although they state that this curve has not been mentioned before, it is similar to Pardee's M-shaped QRS<sub>2</sub>. They have analyzed those cases showing left axis deviation in which there is a distinctly positive R<sub>3</sub> followed by an S<sub>2</sub>, the upward stroke of which rises above the isoelectric level. All of the present group fit the criteria of Katz and Slater. Cases without the second positive deflection or, unlike those cases of Katz and Slater, those with a second positive deflection of 1 mm. or less were placed in Group A, as were those with a suggestive but not distinct initial upward deflection. Furthermore, I have included no cases with QRS complexes lasting more than 0.10 sec.

This Group B type of curve appeared in 320 (4 per cent) of 8,000 records analyzed by Katz and Slater. In the present series, 40 cases (2.3 per cent) were found in 1,781 records. This lower incidence may be ascribed to many factors. Variations in type of patients (for example, negroes) may play a part. Katz and Slater's patients appear to have been in part bed patients. The present series is composed entirely of ambulatory patients. Furthermore, there were certain differences in the criteria used. Their cases include in part, as evidenced by their Fig. 11, certain examples of definite right bundle-branch block.

Eighty-six per cent of their 50 analyzed cases showed clinical evidence of heart disease. Of the remaining 7 patients, 5 were in the arteriosclerotic age group (40 to 54 years). In the present group of 40 cases, 29 (72.5 per cent) were definitely diseased, while the remaining 11 (27.5 per cent) were not. Again this discrepancy in figures may be ascribed to the factors causing variations in incidence. For example, the removal of those patients with right bundle-branch block would certainly change the ratio of diseased to nondiseased patients.

In three instances the second positive deflection in Lead III was of great amplitude (5 mm. or more). These patients were definitely diseased. The effect of the second positive deflection in these three patients upon Lead II (Fig. 2, *D*), together with its interpretation, will be more clearly understood in the discussion under the heading "General Discussion." The T-wave changes in relationship to the second positive deflection are now under investigation in this laboratory.

The third group, as shown in Fig. 1, *C*, is the so-called Q<sub>3</sub> type of curve in accompaniment with left axis deviation, comprising 33 cases (8 per cent). This figure represents 1.8 per cent of all records reviewed. In appearance the curves differ essentially from those of Group A, and especially Group B, in the absence of an initial upward deflection. Twenty-nine, or 88 per cent, of these records met the criteria for significant Q<sub>3</sub> as laid down by Pardee,<sup>5</sup> that is, normal or left axis deviation of the QRS combined with a large Q<sub>3</sub> which is 25 per cent or more of the largest deflection of the QRS complex in any lead. Twenty-two of the

25 in the diseased group fell into this category. Of the 8 nondiseased patients, 7 fell into this group (88 per cent). Although the present series includes only left axis deviation, omitting 3 pregnant women, 85 per cent of the patients with Pardee's criteria were definitely diseased. Among the 7 nondiseased patients, 3 were pregnant; one was fifty-six years old and showed peripheral vessel sclerosis but no evidence of cardiac abnormalities; and 3 were apparently normal. These 3 were of the hypersthenic habitus.

Pardee<sup>5</sup> suggests that a large  $Q_3$  indicates disease of the left ventricle, while others ascribe it to septal disease. Its occasional occurrence in normal hearts, he states, may be due to unusual distribution of the His bundle and/or to a high position of the diaphragm, as a contributory factor. He found a significant  $Q_3$  in only 2 of 277 records taken from normal hearts. Edeiken and Wolferth<sup>6</sup> found no significant  $Q_3$  in 709 apparently normal college students, but in 1,900 unselected electrocardiograms he found a significant  $Q_3$  in 78 (4.1 per cent) of whom 63 (84 per cent) had definite heart disease, 7 were doubtful, 5 had no heart disease, and 3 were unclassified. Although the present series contains only left axis deviation, the percentage of diseased patients (85) corresponds closely with Edeiken and Wolferth's comparable series. Borg<sup>7</sup> found a deep  $Q_3$  in 78 records taken from 1,819 electrocardiograms, but only one such  $Q_3$  in a normal individual. Willius<sup>8</sup> found this peculiarity in only 3 normal individuals among 300 cases. One of his published records (*Fig. 1*, middle record) and one of Pardee's (*Fig. 1, D*) appear to have an initial upward deflection in Lead III. If this were so, these records do not meet the criteria. However, the several complexes shown in the illustrations are not sufficient for judgment of these records, which must rest upon views of longer strips, to rule out the possibility of muscle tremors and artefacts as a cause of small initial upward deflections. This problem may be a real one, as pointed out by Fenichel and Kugell.<sup>9</sup>

The tracings of Cohn and Raisbeck,<sup>10</sup> taken by rotating the leads upon the normal subject to produce the effect of counterclockwise motion of the heart (left axis deviation), show the occurrence of a large  $Q_3$  (Cohn's *Figs. 4 and 5*). In Edeiken and Wolferth's group of pregnant women, two typical  $Q_3$  curves in late pregnancy disappeared following delivery. Pardee had shown the same change. Feldman and Hill<sup>11</sup> found 5 Q-waves of significance in 36 normal pregnancies. Carr, Hamilton and Palmer<sup>12</sup> in an electrocardiographic study of 342 pregnant women found 17 (4.9 per cent) in whom a significant  $Q_3$  was continuously present. Thirteen of these women showed no definite or suggestive cardiac changes. In 3 (4.2 per cent) of 71 pregnancy records reviewed in the present series, a significant  $Q_3$  was seen. I ascribe the changes, as do others, to changed position of the heart, a "transverse heart," or possibly a rotation of the heart upon its axis or the vertical axis of the body.

Such an explanation would also satisfy the findings in the 3 normal hypersthenic individuals in the present series and agrees with the findings of Cohn and Raisbeck. These curves are no doubt variants of the changes described in Groups A, B, and D, due to changes in cardiac position. Such findings cast no doubt upon the genuineness of the meaning of the  $Q_3$  in coronary disease but emphasize the importance of the evaluation of the electrocardiogram not by itself but in terms of the individual patient.

I shall again consider the  $Q_3$  curve under general discussion.

The second most frequent type of curve encountered was that of the pattern shown in Fig. 1, *D*. This type of curve combines the presence of left axis deviation with a definite  $S_2$  of varying amplitude, with  $S_1$  absent or smaller than  $S_2$ . There were 152 such patients, representing 35.2 per cent of the entire group. Of these, 71.1 per cent were definitely diseased, 28.9 per cent were not. In comparison with Group A, it will be seen that 71.1 per cent of the patients were definitely diseased, as opposed to 48.4 per cent in absence of the  $S_2$  (Fig. 1, *A*). The presence of  $S_2$  then distinctly increased the possibility of the presence of heart disease from 48.4 per cent to 71.1 per cent in this series.

An attempt has been made recently to analyze certain of the members of this broad group in association with the presence of other defects.<sup>2</sup> The criteria used in that study were: (1) an inverted or low erect  $T_1$ , less than one-seventh of the R-wave; (2) an  $S_2$  of at least one-half the amplitude of  $R_2$ ; and (3) an erect  $T_2$  greater than  $T_1$ . Proger and Minnich<sup>2</sup> found 40 such records in 136 cases of left axis deviation. Thirty-eight (95 per cent) of their patients had obvious heart disease, an incidence of disease "sufficiently striking to warrant considering such electrocardiograms regularly as distinctly abnormal." In the present series the incidence of such a combination of findings is much smaller, 32 (7.4 per cent) in 431 cases. In 30 (93.7 per cent) of the 32 patients definite heart disease was demonstrable clinically. One patient was, to all methods of examination, entirely normal and another, without demonstrable heart disease, has definite carcinoma of the bronchus with cardiac displacement, which may account for the findings. This analysis in general supports and confirms the findings of Proger and Minnich. In their discussion of the significance of the prominent S-wave in Lead II, they offer no acceptable explanation but consider the possibility of its association with cardiac abnormalities in the manner of T-wave disturbances. An attack upon the explanation of this problem will be outlined later under "General Discussion." I have included in this group two curves classed in Fig. 1, *E*, both falling in the diseased group and both meeting Proger's criteria.

The group taking the configuration seen in Fig. 1, *E*, occurring with  $R_2$  greater than  $R_1$ , violates a usual principle of left axis deviation. Of

course, the major deflection is definitely down in Lead III and up in Lead I. In this group,  $S_2$  was always present, and I believe that the downward deflection in Lead III is distinctly different from that in the previous groups. Of 23 patients (5.3 per cent of all curves analyzed), 2 (8.7 per cent) were not diseased, and 21 (91.3 per cent) were.

Three tracings (0.7 per cent) showed the form portrayed in Fig. 1, *F*. Two of the patients were diseased, one was not.

The final typical picture seen was that shown in Fig. 1, *G*. This group showed left axis deviation with the upward deflection in Lead II conforming closely in height and outline to that of Lead III and, conversely, the major deflection downward in Lead II but always smaller than that

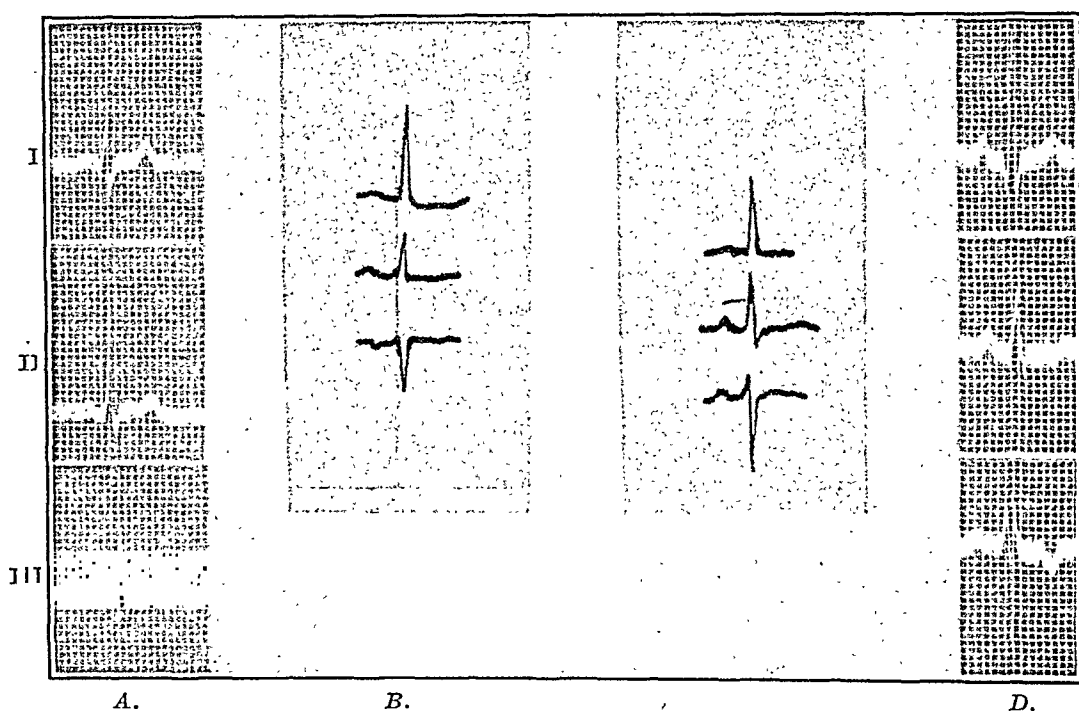


Fig. 2.—A, normal electrocardiogram; B, C, tracings of simultaneous curves taken from Groedel (Das Elektrokardiogramm, Vol. II, Plates 166, 83); D, curve illustrating extreme case falling into Group B.

in Lead III. The positive deflections in Leads II and III were usually of low amplitude with rounded peaks and considerable thickening. Eight such curves (88.9 per cent) were recorded from patients with hypertension and definitely enlarged hearts. One (11.1 per cent) was found in a normal individual, as studied clinically and roentgenologically.

Twelve records (2.8 per cent) (Table I, H) showed bizarre tracings which do not fit any of the classes described and had no constant characteristics. Although the group is a miscellaneous one, including notching and splintering of QRS<sub>3</sub>, into which, as far as analysis is concerned, one may place Group F, a larger series may disclose members with constant characteristics which will demand establishment of categories of their own.



## GENERAL DISCUSSION

A glance at Fig. 1 will disclose a resemblance between some of these curves and those with normal axis deviation. Lead III of Fig. 1, *A*, for example, might well be a complete inversion of the ventricular complex as compared with Fig. 2, *A*. If one assumes that  $R_2$  may become inverted, the possibility exists of the main downward deflection being a Q-wave, an inverted R, an S, or a combination of these three. Einthoven<sup>13</sup> called the chief downward deflection in left axis deviation an inverted R, and today on the Continent this nomenclature is found. Lewis preferred to call this wave an S, and the English-speaking peoples have adhered to his nomenclature. Herrmann and Wilson<sup>14</sup> state that it is unquestionably true that this deflection is produced by the same muscle activity that gives rise in the same cases to the exaggerated  $R_1$ , and that we have no more right to call it "S" than we have to call the inverted  $R_1$  of dextrocardia "S" but that it is convenient to avoid speaking of inverted deflections. It appears more confusing to the author, however, to call a wave "Q" at one time and "S" at another, when it is really chiefly R-wave in both cases, and to designate a wave Q or S in different curves when it signifies the same physiological or pathological processes. If one is to discuss the significance of a Q-, R- or S-wave in diagnosis, he must, for intelligent results, refer to the same process each time. Since this appears to be impossible according to Lewis' nomenclature, the author prefers the nomenclature of Einthoven, which has been advocated recently in this country by Hurxthal.<sup>15</sup>

I have chosen to designate Lead III in relationship to the nomenclature of Lead I, which is almost without exception uniformly consistent. This plan involves the designation of time intervals in Leads II and III rather than upward or downward deflections with the letters Q, R, and S. It is best carried out with simultaneous registration of the three leads, or, at least, of Leads I and II, and I and III. However, it may be carried out in routine curves, as usually taken, by the application of Einthoven's principle: Lead II = Lead I + Lead III. Since allowance must be made for changes due to respiration and the resultant shift in cardiac position, to changes in skin resistance, and to errors in standardization, one cannot analyze routine curves in minute detail. However, a comparison of such an analysis with one of simultaneous curves has convinced the author that little difficulty is usually experienced in assigning a proper name and time interval to the several deflections. While this technic leads to the terms "inverted Q, R, and  $S_2$  and  $S_3$ ", rather than adding confusion to the analysis, the method really clarifies and explains the occurrence of bizarre complexes, especially in Lead II, and carries us closer to the real significance of the slurring and notching we often see.

Fig. 2, *B*, is a reproduction of a curve taken with simultaneous Leads I and II, and I and III. This tracing in appearance has the character-

istics of Group A. It can be seen that  $R_1 + "S_3" = R_2$ ; that  $R_1 + "R_3" \neq R_2$ . The first upward deflection in Lead III may be seen as a slurring and almost a notching at the base of  $R_2$ . The explanation of this slurring then requires a study of the first upward deflection of Lead III, a wave which corresponds in time with the Q time phase of Lead I, and consequently is more truly an inverted  $Q_3$ . Since this small wave in Lead III, an upright wave corresponding to the Q time interval in Lead I, has no known clinical significance, one can realize why we have learned by experience that slurring near the isopotential line, as seen in Lead II, is of no diagnostic importance. The reduced height of  $R_2$ , as compared with  $R_1$  and  $R_3$ , proves this complex to represent, at least in great part, the same electrical phenomenon. In general, the curves of Group A fell into this type and appear to be in a great part inversions of Lead III to form left axis deviation. Often there was a slight second positive deflection in Lead III and frequent inversions of  $P_3$  and  $T_3$ , indicating entire inversions of this lead. Application of Einthoven's principles to these curves, however, shows that the complexes do not always add. This is due to a slight phase difference of the R spikes. That is, the waves of Lead III do not represent precisely the same time interval. Usually the inverted  $R_3$  lags behind  $R_1$ , that is, it encroaches upon the S segment not only in its peak, but in a widening of the upstroke. That the S time interval is only slightly represented, however, is evident in the absence of  $S_2$ , for with Einthoven's rule one would expect an unopposed  $S_3$  to make evident an  $S_2$ . This is precisely the case in the curves of Type D. A reproduction of another simultaneous curve (Fig. 2, C) demonstrates the effect of the S element in Lead III upon Lead II. In the present analysis of tracings, I have used the presence of  $S_2$  as distinct evidence of the presence of an important S element in the downward deflection of Lead III. At times the absence of  $S_2$  in the presence of  $S_3$  is entirely due to a slurring down of  $R_1$  with elevation above the base line during this time phase. When  $S_2$  appeared to represent the same phenomenon as  $S_1$ , the curve was placed in Group A and not Group D. Proger and Minnich were unable to explain the presence and significance of  $S_2$ . It appears from this analysis that the solution lies not in the explanation of  $S_2$  but in the explanation of  $S_3$ .

Of interest here, too, is an explanation of the notching of  $R_2$  in curves of Group B, especially when the second positive deflection is of great size (Fig. 2, D). The notching of the downstroke of  $R_2$ , occurring in the S time interval, represents the effect of the electrical phenomenon describing the second positive deflection of Lead III. Similarly in curves with a less prominent deflection in Lead III the downstroke of  $R_2$  appears as a slight thickening with irregularities identical with those of the wave in Lead III. The QRS width in Lead II can be seen to be increased over that of Lead I to include this time interval. The same analysis holds for Lead II and the upward deflection of Lead III in

curves of the " $Q_3$ " type. This wave occurs at the time interval corresponding to the second positive deflection in curves of Group B. Yet this wave, representing simultaneous and apparently comparable phenomena in each type of curve, is called R in one case and goes unnamed in the other. This wave, as will be seen presently, appears more characteristic of " $Q_3$ " types of curve than is the Q-wave itself.

Further application of the above method of analysis to the  $Q_3$  type of curve described by Pardee discloses difficulties in interpretation. In none of the tracings of this type in the present series did " $Q_3$ " +  $Q_1$  =  $Q_2$ . " $Q_3$ ," in a large part, occupied the time interval of  $R_2$ , i.e.,  $R_2$  equaled more closely  $R_1$  + " $Q_3$ ," indicating that the so-called  $Q_3$  in this type of curve represented more closely the time interval of  $R_1$  than  $Q_1$  or  $Q_2$ . In many cases the downstroke of " $Q_3$ " began in the  $Q_1$  time interval so that the " $Q_3$ " represented a wave occupying both the Q and R time intervals of Lead I. In these curves a  $Q_2$  was always present unless the upstroke of  $R_1$  included this interval with a positive potential. Others of the " $Q_3$ " type of curves appeared identical with those of Group B and, in two cases, of Group A, except for the absence of the first small upward deflection in each instance. A review of the literature indicates that Shookhoff and Douglas<sup>16</sup> have also noted these changes. They have noted also that as  $Q_3$  becomes larger, " $R_3$ " becomes smaller, and " $S_3$ " disappears; and the  $R_3$  corresponds in time to  $S_1$  and represents the same ventricular activity, as I have stated above. Furthermore, in normal electrocardiograms they found that a small  $Q_3$  invariably corresponded to  $Q_1$  and 2, indicating, with the above two types of " $Q_3$ ," three possible groups: (1) those corresponding to  $Q_1$  and  $Q_2$ , (2) those corresponding to  $Q_1$  and part of  $R_1$ , and (3) those corresponding to  $R_1$  in time. I agree, therefore, with the statement of Shookhoff and Douglas that the theories of Lewis and Wilson relative to the inscription of the normal  $Q_3$  may apply only in part to the  $Q_3$  of Pardee. The  $Q_3$  of Pardee can hardly represent always the electrical phenomena of a definite portion of the cardiac musculature. That it may represent occasionally an unusual degree or type of cardiac displacement (rotation about the cardiac or bodily vertical axis) is evidenced by the infrequency with which it is met in normal individuals. Of types of axis deviation due to cardiac displacement, Group A seems to represent that of minor degrees, Group D that of a more marked degree, then Group B, and lastly Group C (Pardee). The percentages of diseased patients in these groups are 48.4 per cent, 71 per cent, 72.5 per cent and 85 per cent, respectively. One would expect that, were such curve types possible in health and disease, the less frequently one occurred in health, the more frequently proportionately would it be found in disease, and that hypersthenic patients falling into Group A in health might, with cardiac hypertrophy, change to one of the other types.

The remaining two distinct types of curves represent configurations which I have not met in patients with obesity and the hypersthenic habitus except in the presence of disease.

In Group E, a determination of the electrical angle of the R time interval indicates the presence of a positive angle, while that of the S time interval, a negative angle. This group is not, in a true sense, left axis deviation even though the major deflection is upward in Lead I and downward in Lead III. The height of  $R_2$  distinguishes this fact at a glance. I have, however, included this group because of its resemblance to left axis deviation and because it illustrates clearly the differentiation between a true R- and a true S-wave in Lead III. This group always displayed an  $S_2$  which was smaller than  $S_3$ , due in part to the fact that the  $S_1$  interval was sometimes above the isopotential line. In this group the major downward deflection was almost entirely  $S_3$ , in contrast to Group D, in which the wave represents in part both R and S.

One also notes that as the S-wave becomes more dominant, it is found in a higher percentage of patients who are diseased. In the present group 21 (86.4 per cent) of 23 patients were definitely diseased. Of the remaining two, one had no clinical evidence of any type of cardiovascular disease. The other, a woman aged sixty-two years, showed evidence of peripheral arteriosclerosis with trophic skin changes and had a persistent blood pressure of approximately 158/82 and mild dyspnea on exertion. However, no objective signs of cardiac disease could be elicited.

In classifying this group care must be taken to rule out records with a prominent  $S_3$  which approaches but does not exceed  $R_3$ . Those tracings in which  $S_3$  did not exceed  $R_3$  in all phases of normal respiration were also excluded.  $S_1$  was not noted in this group. Inverted  $T_{1+2}$ , as noted in Fig. 1, E, occurred five times in this group.

As with Group E, curves of the type of Group G were found in no normal patients of the hypersthenic habitus, and I am able to ascribe neither of these types to changes in cardiac position alone. Lead II of Group G shows an entire inversion of the R time phase. Correspondingly the R and S phases of Lead III are downward. The apices of the major deflections in Leads II and III lag slightly behind the apex of  $R_1$ . The initial upward deflections of Leads II and III correspond in time to  $Q_1$ , and, in curves displaying  $Q_1$ ,  $Q_1$  plus  $Q_3$  was seen to equal  $Q_2$ . Eight of the nine patients with this type of curve were definitely diseased. The remaining patient was a twenty-two-year-old medical student whose history, physical examination, and roentgen ray study were all negative for heart disease.

## SUMMARY

In 431 records showing the major deflection upward in Lead I and downward in Lead III, the QRS configuration in 419 could be grouped into seven distinct types. While four of these types (A, B, C, D) appear to occur in various degrees and types of cardiac displacement, the frequency with which disease accompanies them varies greatly, especially with changes in the Q and S components. Other types of curves (E and G), apparently not related to cardiac displacement, appear much more frequently in diseased than in normal individuals. However, a larger series of these curves is necessary in order to evaluate them accurately. Group E does not rightfully fall into the group of left axis deviation.

## REFERENCES

1. Criteria for the Classification and Diagnosis of Heart Disease, New York Tuberculosis & Health Association, ed. 3, New York, 1932.
2. Proger, S. H., and Minnich, W. R.: Left Axis Deviation With and Without Heart Disease, *Am. J. M. Sc.* 189: 674, 1935.
3. Proger, S. H.: The Electrocardiogram in Obesity, *Arch. Int. Med.* 47: 64, 1931.
4. Katz, S. M., and Slater, S. R.: The Second Positive Wave of the QRS Complex, *Arch. Int. Med.* 55: 86, 1935.
5. Pardee, H. E. B.: Significance of Electrocardiograms With Large Q in Lead III, *Arch. Int. Med.* 46: 470, 1930.
6. Edeiken, J., and Wolferth, C. C.: The Incidence and Significance of the Deep Q-Wave in Lead III of the Electrocardiogram, *AM. HEART J.* 7: 695, 1932.
7. Borg, J. F.: Observations on the Deep Q-Wave in Lead III of the Electrocardiogram, *Minnesota Med.* 16: 694, 1933.
8. Willius, F. A.: Occurrence and Significance of Electrocardiograms Displaying Large Q-Waves in Lead III, *AM. HEART J.* 6: 723, 1931.
9. Fenichel, N. M., and Kugell, V. H.: The Large Q-Wave of the Electrocardiogram, *AM. HEART J.* 7: 235, 1932.
10. Cohn, A. E., and Raisbeck, M. I.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9: 311, 1921-22.
11. Feldman, L., and Hill, H. H.: The Electrocardiogram of the Normal Heart in Pregnancy, *AM. HEART J.* 10: 110, 1934.
12. Carr, F. B., Hamilton, B. E., and Palmer, R. S.: Significance of Large Q in Lead III of the Electrocardiogram During Pregnancy, *AM. HEART J.* 8: 519, 1933.
13. Einthoven, W.: Cited by Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy, *Heart* 9: 91, 1921-22.
14. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy, *Heart* 9: 91, 1921-22.
15. Hurxthal, L. M.: The Identification of the Separate Components of the QRS Complex, *AM. HEART J.* 9: 238, 1933.
16. Shookhoff, C., and Douglas, A. H.: The "Q" Deflection in the Normal and Abnormal Human Electrocardiogram, *Ann. Int. Med.* 8: 177, 1934.

## ECTOPIC TACHYCARDIA, AURICULAR IN ORIGIN, OF UNUSUAL DURATION\*

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IT IS well known that the duration of paroxysmal auricular tachycardia is usually brief and is characterized by an abrupt onset and sudden cessation.

Recently we have had the opportunity of studying two patients whose electrocardiograms are identical with those considered characteristic of paroxysmal auricular tachycardia. In one of these patients a cardiac rate of approximately 140 per minute has been present nearly continuously for forty-three years; in the other patient a rate of 120 probably has persisted for ten years.

Paroxysmal auricular tachycardia was first described by Bristow<sup>1</sup> in 1888. In 1899 Bouveret<sup>2</sup> definitely separated paroxysmal tachycardia from the confused group of cases with simple sinus tachycardia. Vaquez<sup>3</sup> stated that the term "paroxysmal" is somewhat "artificial," as the "various attacks may be long or short; it is not its duration but the manner of evolution that should be considered." The disorder may occur in apparently normal individuals or in those with diseased hearts. It is not known whether hidden pathological lesions in the auricular musculature, abnormalities of the cardiac nerves, or lesions in the central nervous system initiate an attack. Usually there is an abrupt onset of tachycardia with regular beating of the heart (the rate is usually between 120 and 200). Some patients are able to carry on their occupations, while others may be affected by precordial pain, anxiety, and dyspnea. In prolonged attacks, especially in patients with organic heart disease, congestive failure and occasionally death ensue. In the average case, however, there is little dyspnea or discomfort in spite of the extremely rapid heart rate.

Lewis,<sup>4</sup> in discussing the duration of paroxysmal tachycardia, stated, "The attack, except in the very rarest instances, does not last beyond ten or fourteen days." White<sup>5</sup> remarked that the duration of paroxysmal auricular tachycardia was usually "a few seconds or a few minutes, sometimes occurring but once and sometimes repeatedly over a short space of time (a few days or weeks)."

Wilson and Herrmann<sup>5</sup> reported a case of ectopic tachycardia with the history of accelerated pulse of fifteen months' duration. Normal rhythm could be established for brief periods in this patient by digitalis administration and voluntary increase of intraabdominal pressure.

Speroni and Rey<sup>6</sup> described a patient with an electrocardiogram demonstrating paroxysmal auricular tachycardia, who had suffered re-

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peated attacks for twenty years. Autopsy showed the cause of death to be acute yellow atrophy of the liver. There was also rheumatic heart disease.

We have had the opportunity to observe two patients with auricular tachycardia of remarkable duration and have thought it worth while to describe these cases in some detail.

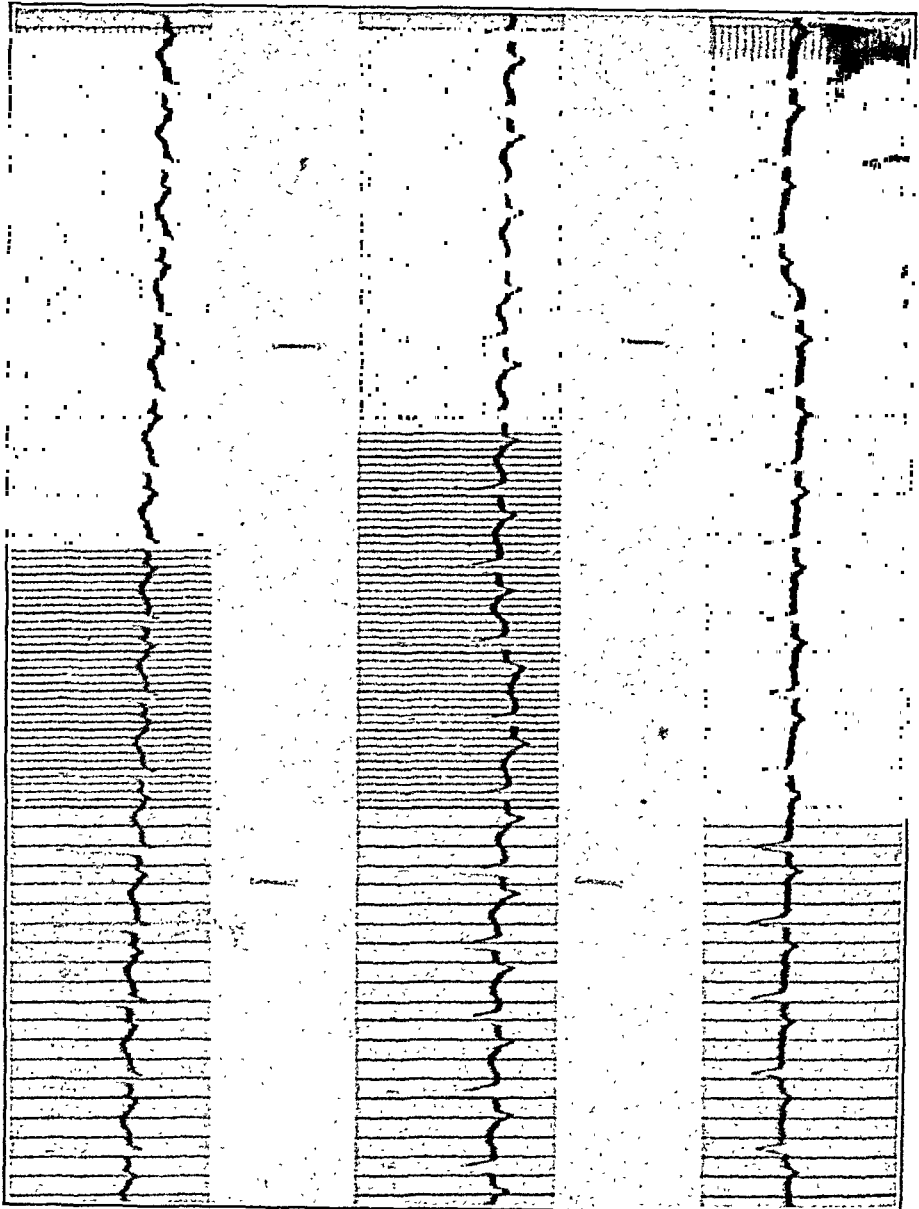


Fig. 1.—May 22, 1933. Tachycardia of auricular origin. Rhythm regular.

#### REPORT OF CASES

CASE 1.—Mr. A. A., aged fifty-nine years, presented himself May 22, 1933, complaining of an old sacroiliac strain and discomfort in the right side of the abdomen. During the examination he remarked that he had had rapid heart action for a number of years, but that he did not have any symptoms referable to his heart. He was leading an active business life and played golf frequently without

discomfort. On further questioning it was ascertained that in 1893, at the age of nineteen years, following an attack of malaria, he developed a "fast heart." He recalled that his pulse rate was 132 at that time. *He was kept in bed for six months and was given digitalis part of the time, but the rapid heart action continued at the same rate.*

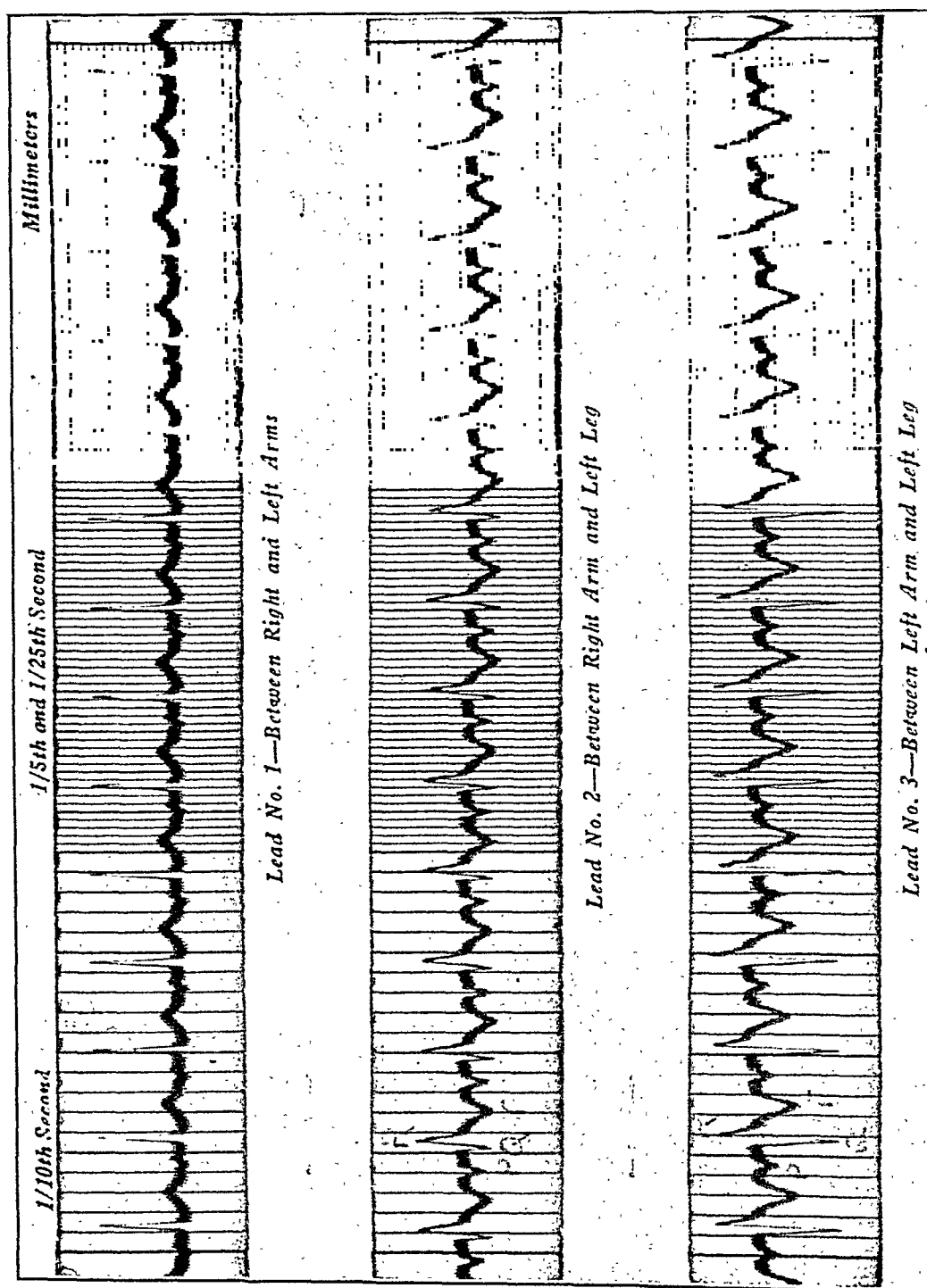


Fig. 2.—May 17, 1935. Auricular tachycardia, rate 140, four weeks after a characteristic attack of coronary occlusion. The elevated RS-T segments and negative T-waves in Leads II and III are suggestive of infarction of the posterior portion of the left ventricle.

Subsequently there were no symptoms referable to the heart, but, after failing to pass a life insurance examination, he consulted Dr. Alfred Friedlander, of Cincinnati, on January 29, 1916. The findings at that time showed the heart size to be within normal limits, the rate was 132, and rhythm was regular. The blood pressure was 124/74. On Feb. 24, 1919, the heart rate was 132, and on March 17, 1919, the rate was 124.



Following the examinations in 1916 and 1919 he had felt well. There was no palpitation, precordial pain, or dyspnea during the intervening years. He believed that the rapid heart rate had persisted continuously since its onset.

The examination on May 22, 1933, showed that the patient was a stocky man of fifty-nine years, weighing 155 pounds and measuring 5 feet 4½ inches in height. The heart borders were 10 × 4 cm., R.S.D. 6 cm. The heart rate was 174, regular,

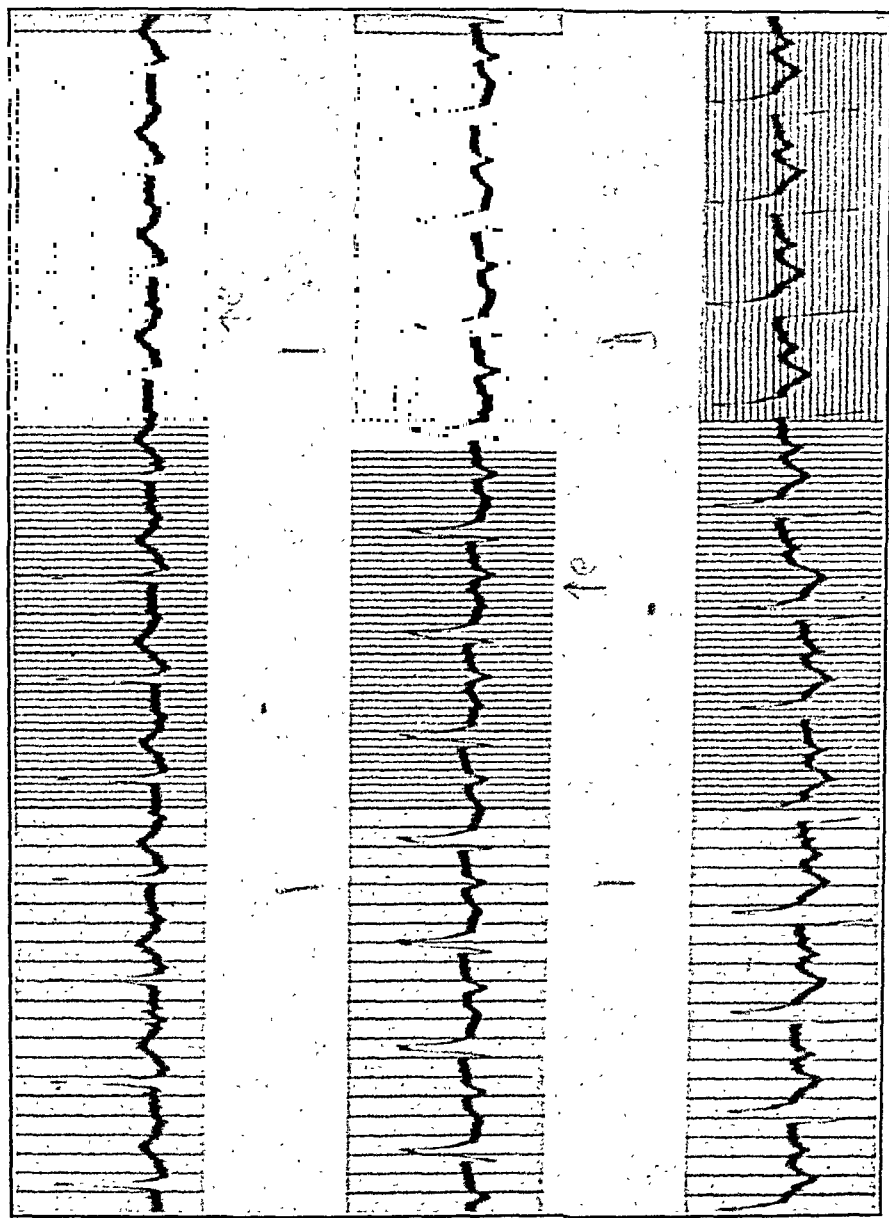


Fig. 3.—Nov. 25, 1935. Rate of auricular tachycardia now only 120 with prolonged conduction time (P-R 0.24 sec.). There is the prominence of Q<sub>2</sub> and Q<sub>3</sub> so often associated with previous infarction. The inverted P-waves are superimposed on negative T-waves in Leads II and III.

no murmurs were heard; A<sub>2</sub> was greater than P<sub>2</sub>. Blood pressure was 170/90. The chest was clear to percussion and auscultation. The abdomen was soft; the liver edge was felt below the costal margin. The spleen was not felt. An electrocardiogram was made May 22, 1933, and is reproduced in Fig. 1. It is characteristic of paroxysmal auricular tachycardia, the rate 160. A teleroentgenogram of the heart was normal.

The patient was hospitalized and, while in the hospital, a horseshoe kidney was demonstrated with evidence of infection in the urinary tract. There was also an obstruction, reported as characteristic of the stricture described by Hunner, in the



woman who did not appear to be ill. She was slightly under her ideal weight. The temperature was 97° F., blood pressure 100/60, pulse 120. The physical examination was essentially negative except for the presence of a soft systolic murmur at the apex of the heart. There was no enlargement of the heart, and the rhythm was regular. The lungs were normal. The liver and the spleen were not felt.

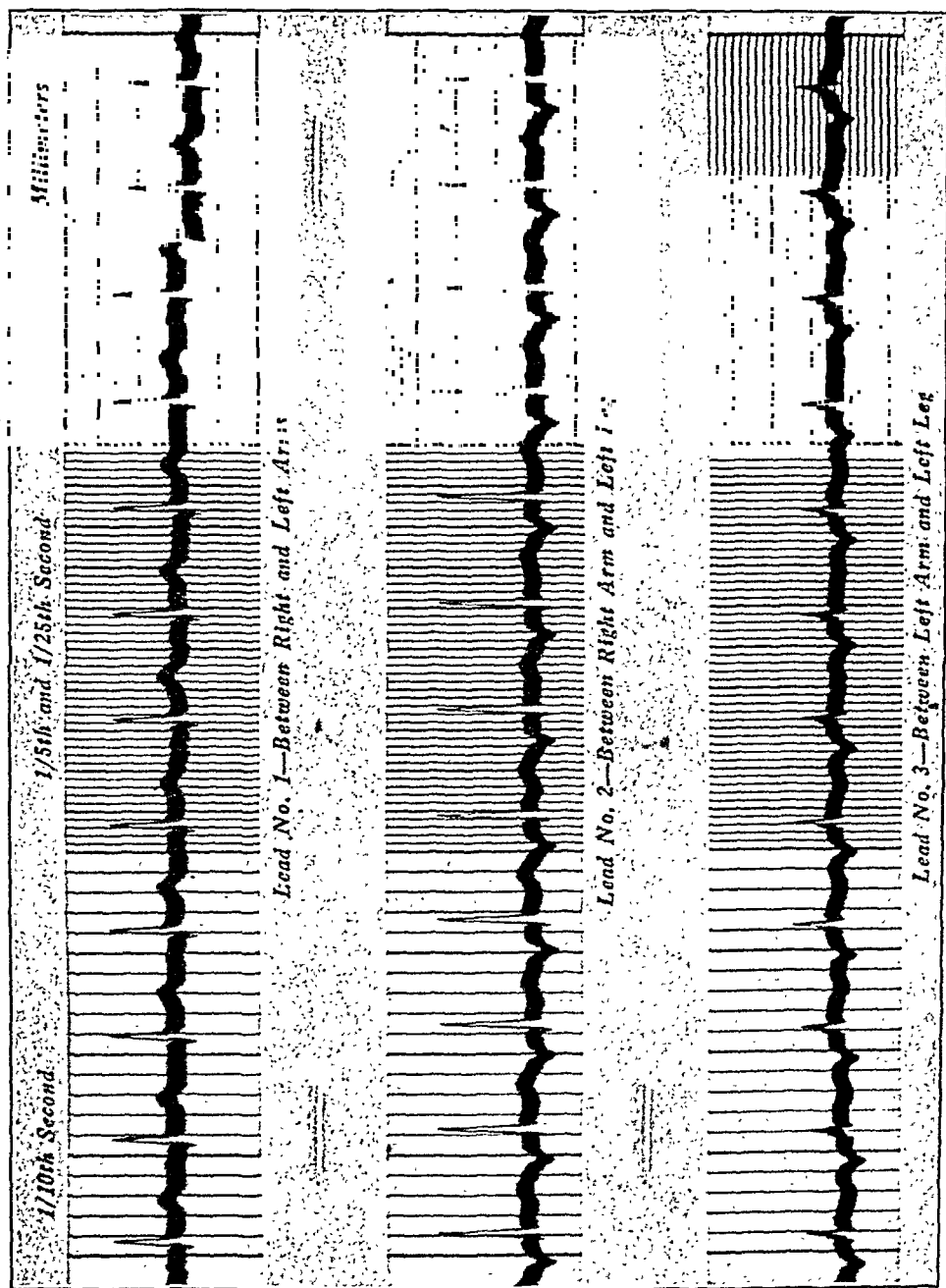


Fig. 4.—Auricular tachycardia. Rate 120. RS-T segment of Lead I is slightly high in origin.

There was no edema of the ankles. A teleroentgenogram showed the heart to be of normal size and configuration. The basal metabolic rate was -15 per cent. An electrocardiogram, Fig. 4, showed the characteristic evidence of paroxysmal auricular tachycardia, rate 120.

The patient was asked to count her pulse at two-hour-intervals and to keep a record of the results. She was assured of the harmlessness of the condition in the presence of a normal heart.

The rate persisted at approximately 120, save on the following morning, when she counted the pulse at 76 immediately on awakening. In a few minutes the pulse returned to its usual rate of 120.

Three weeks later one of us (J. McG.) had the opportunity to see the patient. The pulse was 120 and regular. As she was leaving the city permanently that afternoon, she refused to have another electrocardiogram made. Subsequent efforts to secure information regarding the heart rate have been unsuccessful, but the patient has recently successfully gone through a pregnancy.

#### DISCUSSION

Two patients have been described with ectopic auricular tachycardia of many years' duration. In neither case was there cardiac hypertrophy or evidence of myocardial insufficiency. In both patients the electrocardiograms were identical with those universally considered characteristic of auricular paroxysmal tachycardia.

Tachycardia, of sinus origin, with rates of 120 or over, rarely is encountered save in the presence of febrile illnesses, thyrotoxicosis, auricular flutter, or neurocirculatory asthenia. The clinical and electrocardiographic findings exclude any such factors in our cases. As to the influence of normal sinus tachycardia of equivalent rate and duration upon cardiac function, clinical experience with cases of neurocirculatory asthenia perhaps affords the best basis for comparison. However, in such cases there is always relative slowing during sleep. The possibility of regular reversion to normal rhythm during sleep in our second case must be considered.

Certain conclusions seem obvious: (1) that cardiac rates of 150 or below are not dangerous per se, even when existing for years, in the presence of an otherwise normal heart; (2) that the term "paroxysmal auricular tachycardia" in the sense of *transient* cannot always be employed accurately if the diagnosis is made from the electrocardiogram alone.

#### SUMMARY

Two instances of ectopic auricular tachycardia of many years duration have been described.

As far as can be ascertained, these cases are unique.

In neither patient was there evidence of myocardial insufficiency as a result of the tachycardia. One of the patients developed a coronary occlusion associated with temporary slowing of the heart rate but survived the attack despite the reappearance of tachycardia.

#### REFERENCES

1. Bristow, J. S.: On Recurrent Palpitations of Extreme Rapidity in Persons Otherwise Apparently Healthy, *Brain* 10: 164, 1888.
2. Bouveret, L.: De la tachycardia essentielle paroxystique, *Rev. d. méd., Paris* 9: 753, 1889.
3. Vaquez, H. (Translated by Laidlaw, G. F.): Diseases of the Heart, Philadelphia and London, W. B. Saunders Company, p. 498.
4. Lewis, Sir Thomas: Clinical Disorders of the Heart Beat, London, 1925, Shaw & Sons, Ltd., p. 70.
5. White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 639.
6. Speroni, F., and Rey, J. A.: *Semana méd.* 1: 209, 1930.

## CARDIODYNAMIC AND ELECTROCARDIOGRAPHIC CHANGES IN NORMAL PREGNANCY\*

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MUCH has been written about the heart in pregnancy. Most of the literature deals with the clinical aspects of the condition, and it is generally felt that patients with Class I and Class II† A cardiac conditions do well during the course of a pregnancy, and patients with II B and Class III cardiac conditions do poorly. MacKenzie,<sup>1</sup> in his book, *Heart Disease and Pregnancy*, treats this subject almost entirely from the clinical viewpoint and deals with it for the most part in generalities. It was with the hope of establishing more definite criteria that this work was started. It soon became evident, however, that not enough was known about the cardiocirculatory changes in the normal pregnant woman for any conclusion to be drawn with respect to the changes in those pregnant women having heart disease. Although isolated phases of this problem have been studied and reported, complete correlated cardiodynamic and electrocardiographic studies are lacking.

Some of the more pertinent results reported with regard to the electrocardiographic findings in pregnancy are as follows: Jensen and Norgaard<sup>2</sup> reported a tendency toward left axis deviation in the early months of pregnancy with return toward the normal in the latter months of pregnancy. Smith<sup>3</sup> reported a left axis deviation in the eighth month of pregnancy with a return toward the normal just before delivery of the child. Konki<sup>4</sup> reported left axis deviation and T-wave inversion in Lead III during the latter part of pregnancy with return to the normal after delivery. Carr and Palmer<sup>5</sup> reported that the axis shifted to the left during the first two trimesters of pregnancy and then tended to shift to the right during the eighth and ninth month of pregnancy. Carr, Hamilton, and Palmer<sup>6</sup> in another paper stated that the development of a Q<sub>3</sub> was probably an indication of a transverse position of the heart during the course of the pregnancy and not a reliable sign of heart disease. Feldman and Hill<sup>7</sup> taking electrocardiograms on thirty-six normal pregnant women at the eighth and ninth months and comparing these with electrocardiograms taken after delivery concurred with the above mentioned findings.

Nowhere in the literature could a study of the changes occurring in Lead IV during pregnancy be found.

There is even a greater lack of published correlated cardiodynamic findings occurring during the course of pregnancy. Runge<sup>8</sup> found that

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†Classification of Heart Disease, American Heart Association.

the venous pressure in a nongravid woman in the arm and leg was equal. During pregnancy the venous pressure in the leg was higher than that in the ulnar vein, and in the puerperium the venous pressure in the legs dropped far below the venous pressure in the median vein. Spitzer<sup>9</sup> concluded that the circulation time remained within the limits of high normal during the course of pregnancy in the normal woman. Alward<sup>10</sup> taking vital capacities on standing patients reported a gradual reduction during the last month of pregnancy with a gradual return to normal limits at the tenth day of the puerperium. Stander and Cadden<sup>11</sup> found a steady increase in the cardiac output from the fourth month of pregnancy amounting to over 50 per cent of the normal value as the pregnancy advanced, with a return to the normal by the third week of the puerperium.

The reason for the lack of correlated data with regard to the cardio-circulatory changes during the course of pregnancy becomes obvious when viewed in the light of our experience. Forty-four normal pregnant women were studied.

With every possible effort we were able to complete our observations in only nineteen cases. Examinations of some patients were discontinued because of development of urine abnormalities or marked varicosities. Others refused to return after four to six months of observation because of the rather arduous nature of the examination. We found it almost impossible to obtain patients in the first and second months of pregnancy. This lack of control observation was negated by the performance of a follow-up examination on the patients six to eight weeks after their delivery.

#### METHOD OF PROCEDURE

Patients were seen as early as possible during the course of their pregnancy. None was taken for examination after the fourth month. All women selected were normal. Patients who had, or who developed, positive serology, abnormal urinary findings, or abnormal blood findings were excluded.

At the time of first examination a complete history, physical examination, and an x-ray film of the chest were taken. A record was made of the pulse rate, respiratory rate, and blood pressure. Then, a four-lead electrocardiogram was obtained, and vital capacity, intravenous pressure, and circulation time were measured. Care was taken to have the patient rest for thirty minutes before the procedures were started, and the intravenous pressure and circulation time were measured in the order named at the end of the examination so as not to influence the other cardiodynamic findings.

Lateral and anterior x-ray pictures of the chest were taken at the time of deep inspiration in order to rule out, as far as possible, apparent enlargement of the heart due to a transverse position of the organ. The pulse rate, respiratory rate, blood pressure, and vital capacity examinations were recorded with the patient in a sitting position, this being a compromise between the supine and standing positions.

The fourth lead of the four-lead electrocardiograms was taken with the right-arm electrode placed in the fourth interspace just to the left of the sternum and with the left arm electrode placed on the left leg. The authors agree with Katz and Landt<sup>12</sup> that the fourth left intercostal space should be the site of choice for the

right-arm electrode because of the variability of the location of the apex of the heart in different patients. Furthermore, it can readily be seen that an apical fourth lead electrocardiogram would tend to negate any findings with regard to axis shift as the pregnancy advanced. Likewise, we feel that the left leg should be the site of choice for the left arm electrode or indifferent electrode because, as Wilson and his associates<sup>12</sup> have shown, the fourth lead of the electrocardiogram is not appreciably altered by this method. The above mentioned positions of the electrode for the fourth lead are of distinct advantage inasmuch as respiration will not tend to cause a slippage of the electrodes as is encountered when the anteroposterior chest technic is used. The intravenous pressures were taken after the method of Griffith, Chamberlain, and Kitchell.<sup>14</sup> The region of the right cubital vein was anesthetized with 1 per cent procaine solution so as to obviate the pain and the consequent reflex reaction of the circulatory system produced by the injection of the manometer needle. The intravenous pressures were measured with the manometer needle in the cubital vein with the patient in a horizontal position, care being taken to level the vein and the manometer zero reading with the midaxillary line. The midaxillary line is usually accepted as being at the level of the right auricle. After the completion of this procedure the manometer was disconnected from the needle, and a syringe containing 5 c.c. of decholin was attached to the needle. This was injected rapidly, and by means of a stop watch the elapsed time was noted for the appearance of a reaction in the form of a bitter taste in the patient's mouth. The reactions were clear-cut and the grimace of the patient, the signal agreed upon, immediately marked the appearance of the bitter taste. We used decholin because we wished to correlate our work with that of Spitzer,<sup>9</sup> who originally investigated this phase of the problem.

Each patient was seen at monthly intervals following the initial examination and the previously described procedures were carried out except for the x-ray examinations which were made at the time of the initial visit; at the seventh to eighth month of pregnancy and six to eight weeks postpartum. A complete check examination was done six to eight weeks following the delivery. These patients also received monthly examinations in the prenatal clinic, and thus we were furnished with additional evidence as to the condition of the individual.

#### OBSERVATIONS

*History.*—The ages of the nineteen patients studied ranged from seventeen to thirty years. None of them had been seriously ill during their lives, and their past histories were relatively unimportant. They all had had diseases of childhood, but none was left with any residuals. During the course of their pregnancies no untoward complaints were registered. Every one of them stated that from about the fourth month on they noticed progressive tiredness and progressive shortness of breath on exertion. All of the patients developed urinary frequency and nocturia of one to three times per evening from about the fourth month of pregnancy until time of delivery. We were inclined to view the frequent voiding in the light of a decreased bladder capacity as a result of compression by the enlarging uterus. Later in this article we present evidence which shows that a burden is placed on the cardiocirculatory system by the advancing pregnancy which in the normal case is compensated for by the physiological readjustment of that and allied systems. We, therefore, agree with the fundamental concept of MacKenzie,<sup>1</sup> which would explain the symptoms resulting from exercise as being the

effect of another burden superimposed on a system which had been working to the maximum of its functional reserve. From the seventh month of pregnancy until time of delivery, six of the patients gave a history of slight edema of the ankles toward the close of the day. This edema did not appear unless the patient was on her feet for a long period of time (six to eight hours) and was interpreted by us as being the result of uterine pressure on the common iliac veins.

*Physical Examination.*—The changes produced by the advance in pregnancy were of particular interest as evidenced by the physical findings. In all of the nineteen cases there was a progressive increase in accessibility of the right ventricle as noted by palpation over the precordium. Associated with this observation was the fact that, as the pregnancy advanced, the pulmonic second sound became progressively more distinct and the aortic second sound diminished in intensity. Actual statistics of our cases show that the pulmonic second sound became much louder than the aortic second sound in the majority of cases (fifteen), slightly more distinct in three cases, and equal to the aortic second sound in one case. The above findings had their inception about the fourth month of pregnancy, became more manifest until the seventh month, and then remained stationary or decreased slightly until time of delivery.

The increased intensity of the pulmonic second sound could be expected in view of the increased accessibility of the right ventricle to palpation and our x-ray evidence of the encroachment of the right ventricle on the anterior clear space. That the increased pulmonic second sound was not due to increased pressure in the lesser circulation can be indirectly inferred from the intravenous pressures obtained which showed no elevation. The decreased aortic second sound is easily understood when one views the drop in blood pressure associated with the advancing pregnancy.

A systolic murmur was heard over the base of the heart and was localized over the pulmonic area in fourteen of the cases. It was usually first heard in the third to the fourth month, became progressively louder until the seventh to eighth month, and then remained stationary or decreased slightly in intensity until time of delivery. At the time of post-partum examination the systolic murmur, like the other cardiac abnormalities, had disappeared. Two cases developed a split second sound at the base during their pregnancy. In the nineteen cases studied, no murmurs were heard at the apex. One case (Mrs. B. C., No. 20) had a palpable thrill accompanying the systolic murmur at the base. The origin of the systolic murmur at the base is not well understood. The fact that it tended to disappear with deep inspiration may point to a kinking of the pulmonic artery as a causative factor, the kinking being relieved by the descent of the heart with the diaphragm on deep inspiration. On the other hand, the systolic murmur at the base may be of



cardiorespiratory origin. This last interpretation does not explain the pulmonic thrill found in one of the cases reported and two others not included in this series.

Table I condenses these findings.

TABLE I

CASES	SYSTOLIC MURMUR PULMONIC AREA	ACCENTUATED P-2	DECREASED A-2	ACCESSIBLE RT. VENT.	HISTORY OF EDEMA OF ANKLES
1	+	+	+	+	+
2	+	+	+	+	+
3	+	+	+	+	-
7	+	+	+	+	-
8	+	+	+	+	-
10	+	+	+	+	-
11	+	+	+	+	-
15	+	+	+	+	-
17	+	+	+	+	+
18	+	+	+	+	- ← Split second sound at base
20	+	+	+	+	+
22	+	+	+	+	+
23	+	+	+	+	+
24	-	+	+	+	-
12	-	+	+	+	-
19	-	+	+	+	- ← Split second sound at base
21	-	+	+	+	-
27	-	+	+	+	-
29	-	+	+	+	-

← Split second sound at base  
← Systolic thrill pulmonic area

*Blood Pressure.*—If one can consider the final blood pressure taken, at the time of follow-up examination, six to eight weeks following delivery, as being the average normal, it will be noted that the systolic pressures fall in a linear fashion during the first four months of pregnancy. The average fall for nineteen cases was 13 mm. of mercury. The same is true of the diastolic pressures, the average fall for the nineteen cases during the first four months of pregnancy being 17 mm. of mercury. From the fifth to the seventh months of pregnancy the average systolic and diastolic pressures do not change appreciably. From the seventh to the beginning of the ninth month there is a slight but definite rise as shown by the average systolic and diastolic pressures. At the time of post-partum examination the average systolic pressure had risen 11 mm. mercury and the average diastolic 14 mm. mercury. If one scrutinizes the data, one will find that the trend of both systolic and diastolic pressure in each individual case absolutely parallels the reported average trend. A definite explanation for the lowered systolic and diastolic pressures during the height of the pregnancy can be found if one takes into account the enormous blood reservoir created in the pregnant uterus and compares this condition to cases in which slight degrees of splanchnic

dilatation occur. When the process of lightening occurs, the blood reservoir is decreased as a result of pressure exerted by the confines of the pelvis, the rise in systolic and diastolic pressures during the eighth and ninth months being proportioned to this dynamic effect. When the uterus is emptied, the blood reservoir disappears with the delivery of the placenta and six to eight weeks post partum the pressure is again at the norm.

*Pulse and Respiratory Rates.*—The pulse and respiratory rates gradually increase until the seventh month of pregnancy. From the seventh to the eighth month the pulse rate continues to rise while the respiratory

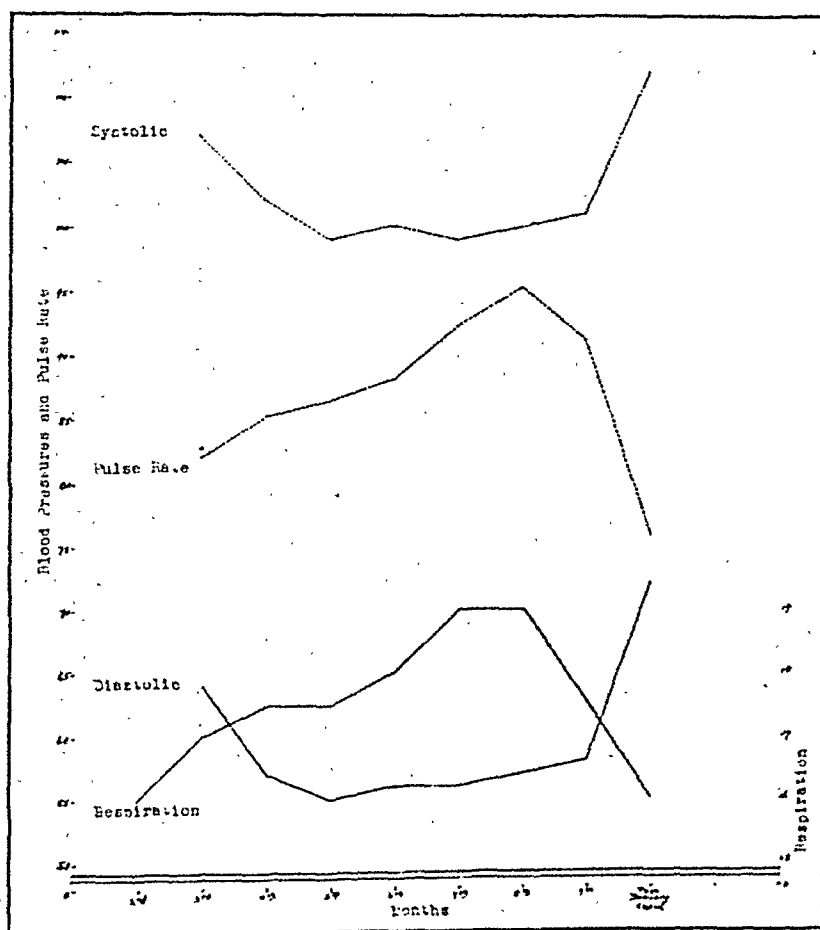


Fig. 1.—Graphic representation of systolic and diastolic blood pressures, pulse rates, and respiration rates through the months of pregnancy.

rate levels off. From the eighth month the trend of both rates is sharply downward until at the time of examination after delivery the average pulse rate was 72 per minute and the average respiratory rate 16 per minute. The trend of the pulse rate and the respiratory rate is an index of an attempt to compensate for an embarrassed circulation. The trend of these two rates again fits in with the picture seen in slight degrees of splanchnic dilatation.

Figure 1 graphically illustrates the trends of the systolic and diastolic pressures and the pulse rate and respiratory rate during the course of pregnancy.

*Intravenous Pressures.*—In general, intravenous pressures had a tendency to start at a fairly high level (80 to 100 cm. of water) in the early months of pregnancy, then decrease until about the sixth to the seventh month and then increase until the time of final examination. Frequently they did not return to the level of the previous highest pressure and in three women remained at the level found during the ninth month. From the data one is justified in stating that in the majority of cases the intravenous pressures are at their lowest about the sixth to the seventh month. The range of the intravenous pressures in all cases did not exceed 48 to 110 cm. of water. If the initial venous pressure was high, the drop during the sixth to the seventh month did not reach the low levels found at the same period in those cases starting with a relatively low initial intravenous pressure. Thus we see that the intravenous pressures fall within the high normal ranges (40 to 140 cm. of water), established by George C. Griffith and his associates,<sup>15</sup> who used the same technic. The tendency of the intravenous pressures to drop during the middle month of the pregnancy seems to coincide with the drop in blood pressures. The tendency toward a slight rise in the intravenous pressures from the seventh to the ninth month also roughly parallels the absolute trend of the blood pressures. However, the trend of the intravenous pressures throughout pregnancy is not nearly as definite as that of the blood pressures. Again one can see the phenomenon of the changing volume of a large blood reservoir mirrored to some extent in the intravenous pressure findings.

*Circulation Time.*—The circulation time ranged from nine to sixteen seconds in the nineteen cases studied. The majority of patients ranged from ten to fourteen seconds. There was no definite trend throughout the course of pregnancy. These findings agree with work of Spitzer<sup>9</sup> and fall within the limits of normal. We feel that the relatively stationary circulation time is a resultant of the previously mentioned trends of blood pressure, intravenous pressure, pulse rate, respiratory rate, and cardiac output. It has been shown by Stander and Cadden<sup>11</sup> that from the fourth month of pregnancy to full term there is a steady increase in cardiac output, amounting to about 50 per cent of the normal. This increase in cardiac output again fits into the picture and may fully be accounted for by the increase in pulse rate without presupposing an associated enlargement of the ventricles.

*Vital Capacity.*—On the whole, the vital capacities on successive months did not show any definite trend during the course of pregnancy. To be sure, there was a monthly variation of 100 to 200 c.c. and in some few isolated instances there was a deviation of as much as 300 c.c. from the preceding month. These variations were in the nature of an increase or a decrease from the mean. For the most part the monthly variations in the vital capacities were not in excess of what one finds in a normal person from day to day.

At first we were of the opinion that the vital capacity of a patient would increase as the pregnancy advanced. Recalling Hoover's<sup>16</sup> work with regard to diaphragmatic excursions we expected this since the dome of the diaphragm is greatly elevated during the course of pregnancy. However, there is a marked increase in the intra-abdominal pressure. Therefore, any given vital capacity must be viewed as a resultant of these contracting forces. Increase or decrease of the vital capacity depends on which force is in ascendancy. This is in turn modified by the patient's position. From clinical and x-ray evidence there can be no doubt that the residual capacity of the lungs is greatly diminished.

*X-ray Examination of Chest.*—The anterior view of the chest showed elevation of the diaphragm from the fourth month on. It must be realized that the x-ray examinations of the chest were done at the height of a deep inspiration. These silhouettes show that during the middle months of pregnancy the diaphragm on both sides was elevated on an average of 2 cm., above the normal. At this time the oblique and transverse diameters of the heart showed a 0.5 cm. to 1 cm. increase over the normal size.

The corresponding lateral views, even at the time of deep inspiration, showed some degree of encroachment on the anterior clear space by the right ventricle. The average increase of the anteroposterior diameter of the heart in the nineteen cases studied during the middle months of pregnancy was about 1 cm., over the normal.

As the pregnancy advanced, the heart was pushed upward and forward. This was to be expected when one recalls that the heart rests for the most part on the left anterior slope of the diaphragm. X-ray silhouettes taken with the patient holding her breath in midtidal respiration showed a marked elevation of the diaphragm and a definite encroachment of the right ventricle on the anterior clear space. It is our opinion that the small increases noted in the various diameters of the heart during deep inspiration cannot be interpreted as being the result of the cardiac enlargement. We feel that they are an expression of a more transverse position of this organ as a result of the average diaphragmatic elevation of 2 cm., encountered at this time. This elevation of the diaphragm agreed with the results of Hynemann,<sup>17</sup> who found that during the early part of the third trimester the right side of the diaphragm was elevated on the average of 2 cm. and the left side of the diaphragm on an average of 2.1 cm. He also noted that the heart had assumed a more transverse position at this time.

In addition to these x-ray findings and their interpretation, our contention that the heart is not enlarged during pregnancy is further supported by the fact that a searching review of our cardiodynamic findings failed to give any evidence which a priori would demand cardiac enlargement for its explanation. In the first place the blood pressures, systolic

and diastolic, fall during the course of the pregnancy. The intravenous pressures, although remaining within the range of the normal, show a tendency to decrease. The rapid pulse rate precludes any increased filling of the heart per beat. We have pointed out that the increased cardiac output can be definitely explained on the basis of increased pulse rate. Finally, it can be inferred that there is no increase in the lesser circulation pressure, both from the reported intravenous pressures and from the fact that the magnitude of the decreased residual capacity of the lungs does not approach that necessary to cause an increase in the lesser circulation pressure.

*The Electrocardiographic Changes.*—The electrocardiograms of the 19 cases comprising this study can be divided into several groups. The types for the most part depend on characteristic or lack of characteristic changes in Lead III. When one views the records, one will find that for practical purposes Leads I and II remain unchanged throughout the course of pregnancy. From the position of the "pick up" electrodes with regard to the shifting heart, it can be readily understood why Leads

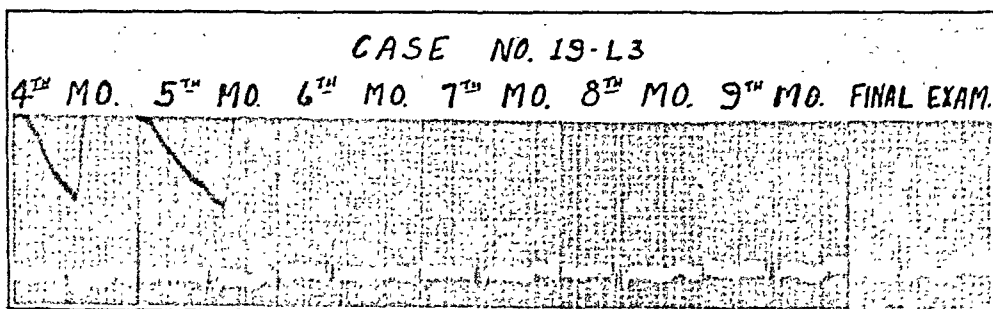


Fig. 2.

I and II tend to remain constant and why Leads III and IV show variations during the period of pregnancy.

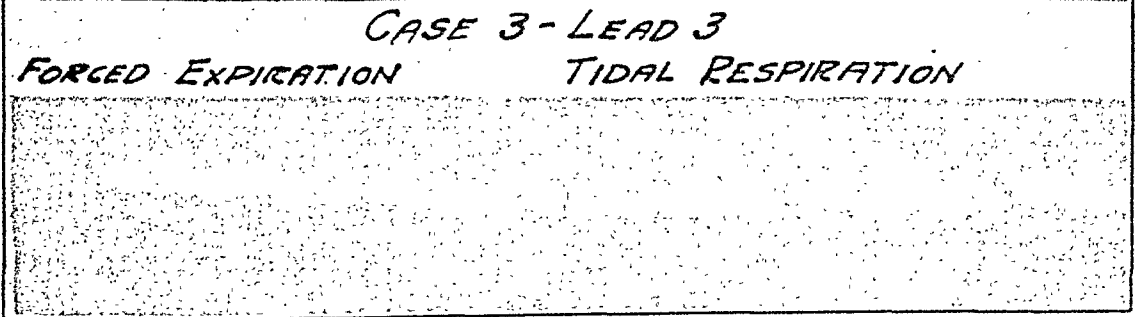
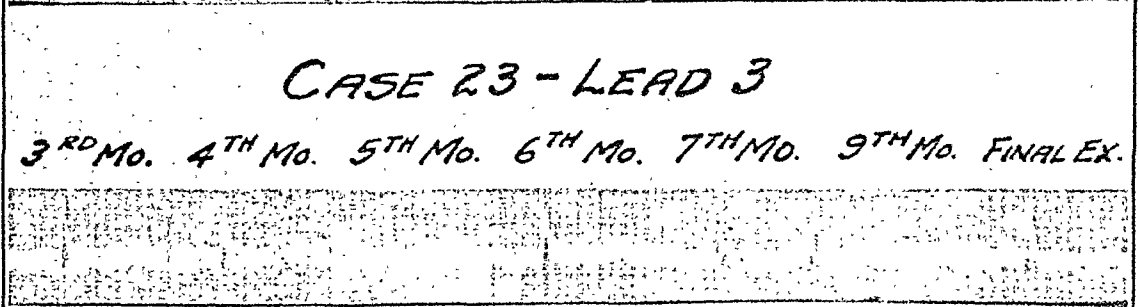
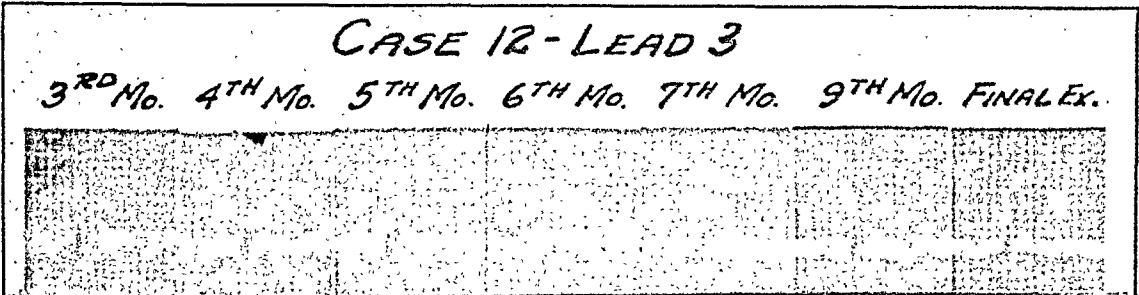
Four cases may be automatically placed in Group I. They showed no appreciable changes with regard to P or QRS deflections throughout the course of the pregnancy. They did show a definite inversion of the T-wave which became apparent at any time from the fourth to the ninth month, which changed from month to month, and which became definitely positive at the time of the final examination. (Cases 2, 8, 17, and 19.) Case 19 shows a series of electrocardiograms characteristic of this group (Fig. 2).

Group II is composed of 12 cases. In general, these cases may be described as showing a tendency toward left axis shift (or actually showing a definite left axis shift).

For purposes of clarity it is necessary to further divide Group II into three subgroups. In Group II A there were six cases (Cases 3, 7, 12, 21, 23, and 27) whose electrocardiograms in Lead III primarily showed a decrease in voltage of the QRS complex (Fig. 3). This group showed

an attendant slurring of the QRS complex in some instances (Cases 3, 7, 23, and 27), and the development of an "ironed out" or inverted T-wave in all six cases. Two of the six cases (Cases 23 and 27) showed a small Q-wave at the time when the voltage was lowest (Fig. 4).

Case 3, which is typical of this group, lends further support to the belief that in this study a progressive lowering of the voltage is the first stage of a definite axis shift. At the eighth month when the QRS was at its lowest voltage and markedly slurred, a forced expiration which lifted the diaphragm higher, produced a definite inverted QRS complex in which the R-wave was absent (Fig. 5).



Group II B is composed of the remaining six cases. These cases present electrocardiograms that show definite left axis shift. Three of these cases (Cases 15, 18, and 22) developed the W-type of wave which in the early months of pregnancy appeared as a normal QRS complex with a small but definite Q- and S-wave. Case 15 demonstrated this type of change. All three cases presented a flattening or inversion of the T-wave some time during the course of the pregnancy, and slurring of the QRS complex (Fig. 6).

The other three cases (Cases 1, 20, and 24) showed the development of a left axis shift during the course of the pregnancy. All three of these had slurring of the QRS complex and two (Cases 1 and 24) show the usual alteration in the T-wave (Fig. 7).

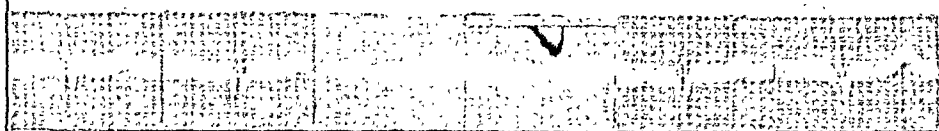
Group III is composed of two cases (Cases 10 and 29) which are distinctly different from the rest. In the earlier months of pregnancy the QRS complex had a diphasic character with the initial Q deflection, although small, being larger than the R deflection. As pregnancy advanced, the voltage increased and the R deflection became larger than the Q until the eighth month of pregnancy, when the original Q deflection was represented by an upstroke of the R deflection. At the time of final examination the QRS complex was again diphasic, the Q being larger than the R. Both of these cases show the usual T-wave changes (Fig. 8).

Group IV was created because the final case (Case 2) could not be placed in any of the preceding groups. Lead III did not change appreciably throughout the pregnancy. The P-wave was inverted throughout the study. The initial deflection of the QRS complex was small and

### CASE 15 - LEAD 3

4TH Mo. 5TH Mo. 6TH Mo. 7TH Mo. 8TH Mo. FINAL Ex.

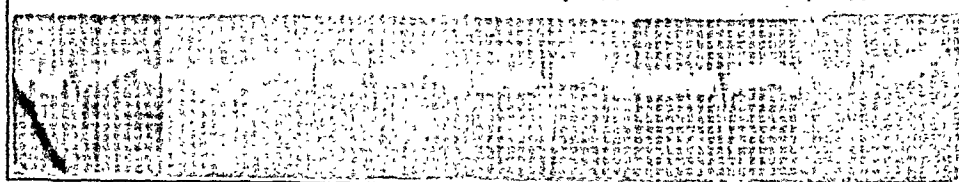
Fig. 6.



### CASE 20 - LEAD 3

4TH Mo. 5TH Mo. 6TH Mo. 7TH Mo. 8TH Mo. FINAL Ex.

Fig. 7.



upright. The major deflection was down and inverted. Actually the QRS complex was diphasic, but it presented the picture of a definite permanent left axis shift.

The T-wave went through the usual changes and at the time of final examination it was diphasic in character. As far as we could ascertain, the patient did not have any heart disease and was perfectly normal (Fig. 9).

In all of the nineteen cases definite changes were noted throughout the course of pregnancy in Lead IV. For the most part these were shown by the shifting of the S-T segment, which had a tendency to change from a negative take-off to an isoelectric take-off and by the T-wave, which became diphasic in some instances, even upright and positive. The QRS complex frequently changed in amplitude during the course of the pregnancy. Quite frequently the initial Q deflection became smaller. Several of the cases showed definite slurring of the QRS complex. Cases 7, 19, and 21 showed these changes (Fig. 10).

The electrocardiographic changes can be explained for the most part on the basis of a left axis shift. Einthoven and his coworkers<sup>18</sup> have shown that the transverse position of the heart at the end of expiration is associated with a tendency toward, or with an actual, left axis deviation as noted in a standard three-lead electrocardiogram. Cohn and Raisbeck<sup>19</sup> have also shown that the left axis deviation in the electrocardiogram is associated with a greater transverse position of the heart and that right axis deviation tends to occur as the position of the heart becomes more vertical. Smith,<sup>3</sup> Konki,<sup>4</sup> Jensen and Norgaard,<sup>2</sup> Carr and

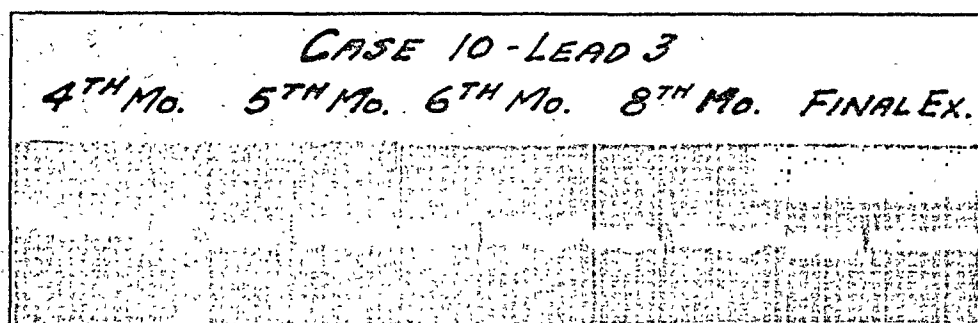


Fig. 8.

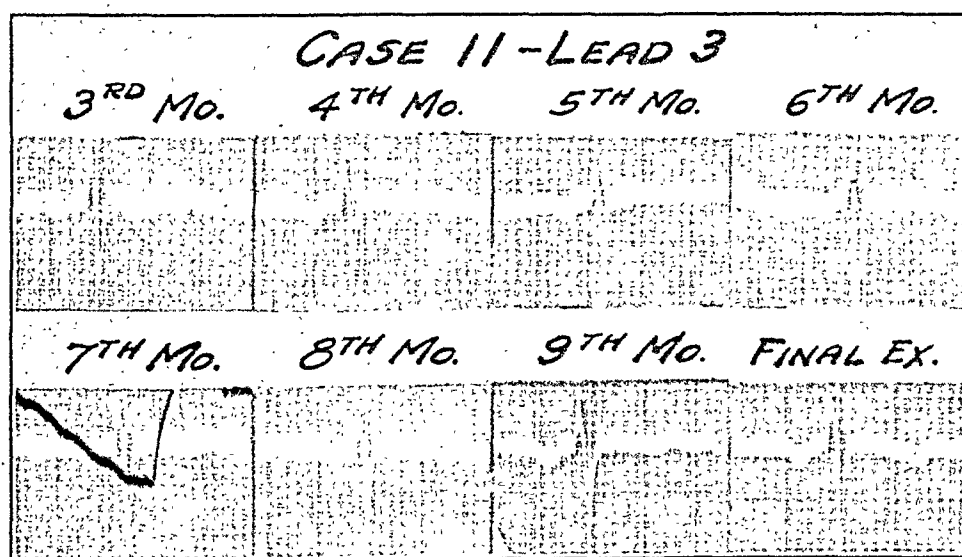


Fig. 9.

Palmer,<sup>5</sup> and Feldman and Hill,<sup>7</sup> from their studies of the conventional three-lead electrocardiogram taken of pregnant women, came to the conclusion that the changes observed are the result of left axis deviation. Feldman and Hill studied electrocardiograms taken at the eighth and ninth months of pregnancy and shortly after delivery. They did not have the opportunity of studying more complete records. The same was true of Carr and Palmer, who, in their article make a plea for a more comprehensive electrocardiographic study of the normal pregnant woman throughout the entire term of pregnancy.

Just why only four of our cases showed T-wave changes during the course of pregnancy is not understandable. However, our findings are



in accord with those of Feldman and Hill, who report  $T_3$  inversions in only four of their thirty-six cases. We feel that the reason for the electrocardiographic changes noted in all of our cases is definitely the result of monthly examination. It might be postulated that the one case that showed a complete left axis deviation throughout the period of pregnancy and at time of final examination belonged in the group showing

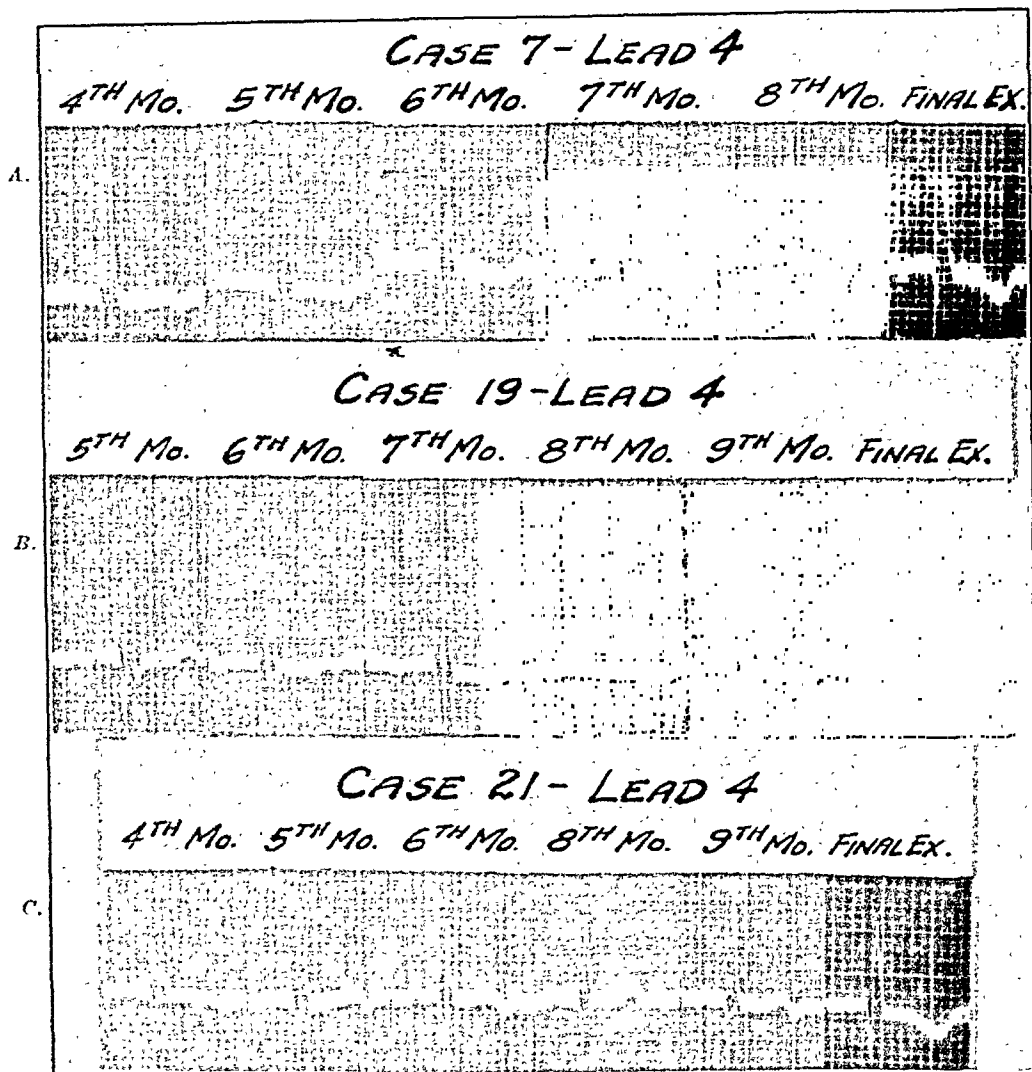


Fig. 10.

$T_3$  changes because the records did show slight changes in the T-wave in Lead III. It is our belief that the development of a Q-wave of various magnitudes during the course of the pregnancy is nothing more than an expression of a left axis shift, and we concur in this belief with Carr, Hamilton, and Palmer.<sup>6</sup> Surely our records cannot be interpreted on any other basis.

The changes noted in Lead IV (S-T and T-wave changes) have already been commented upon. They are of importance because of their

constancy. There were further changes noted with regard to the relationship of the amplitude of the Q- and R-waves which could not be interpreted because of their inconstancy.

It has been stated by several observers that changes, especially the slurring encountered in the electrocardiogram of the pregnant woman, are the result of toxemia. Jensen and Norgaard felt that the electrocardiographic changes in the pregnant woman were due to the alternating hypertrophy of the ventricles. We can show definitely that these two opinions are erroneous. In the first place these two statements are highly improbable when viewed in the light of clinical and cardiodynamic findings of these nineteen normal pregnant women. In the second place, time after time when the third lead showed maximum changes, a normal third lead could be obtained by making the patient take a maximum inspiration. The following record (Fig. 11) illustrates this and renders untenable an organic explanation for the electrocardiographic changes seen during the course of a normal pregnancy (Case 27, Lead III, at ninth month).

Table II summarizes the nineteen case histories.

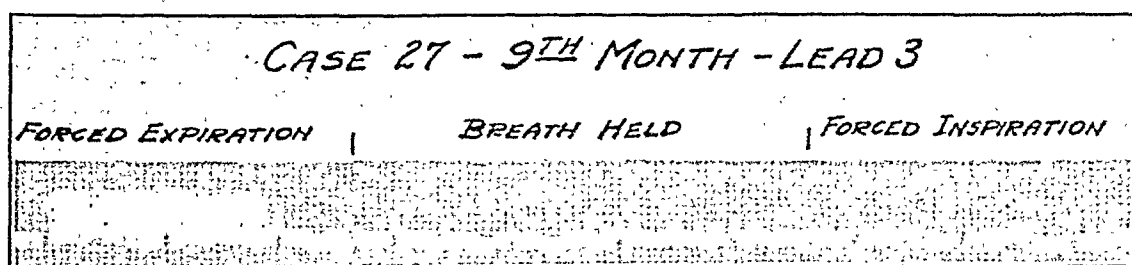


Fig. 11.

#### SUMMARY

Nineteen normal pregnant women were studied throughout the course of their pregnancy, and the final examinations were made from six to eight weeks after delivery. The study included the correlation of clinical, cardiodynamic and electrocardiographic findings during the period of pregnancy and puerperium. The final examination, approximately two months after delivery, was taken as the control for each case.

The correlation of these findings led us to the following conclusions:

1. Pregnancy definitely places a burden on the cardioecirculatory system.
2. In the normal woman this burden is of the magnitude that can be compensated for by calling on the reserve capacity of this system.
3. The method of compensation for the increased burden is both mechanical and physiological in nature.
4. The electrocardiographic changes observed during the course of pregnancy may be definitely interpreted on the basis of mechanical shifting of the heart.

TABLE II  
CASE HISTORIES, IN BRIEF, OF PATIENTS COMPRISING THIS STUDY  
(ALSO SEE TABLE I)

CASE NO.	AGE	PREV. PREG.	MISCAR.	FIRST EXAM.	SEROL.*	DELIVERY	ISSUE	SYMPTOMS	POST-NATAL EXAM.
1	23	multip.	0	3rd mo.	Neg.	Nor.	Nor.	diuria and nocturia ++	No abnormalities
2	24	primip.	0	4th mo.	Neg.	Nor.	Nor.	nausea ++, dyspnea +, diuria	No abnormalities
3	30	multip.	0	3rd mo.	Neg.	Nor.	Nor.		No abnormalities
7	19	primip.	0	4th mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
8	20	multip.	0	4th mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
10	30	multip.	0	4th mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
11	28	multip.	0	3rd mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
12	19	multip.	0	3rd mo.	Neg.	Nor.	Nor.		No abnormalities
15	30	multip.	0	4th mo.	Neg.	Nor.	Nor.	dyspnea, polyuria	No abnormalities
17	26	multip.	0	3rd mo.	Neg.	Nor.	Nor.	nausea, vomiting	No abnormalities
18	29	multip.	0	3rd mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
19	28	multip.	0	4th mo.	Neg.	Nor.	Nor.		No abnormalities
20	18	multip.	0	4th mo.	Neg.	Nor.	Nor.		No abnormalities
21	30	multip.	0	4th mo.	Neg.	Nor.	Nor.		No abnormalities
22	28	multip.	0	3rd mo.	Neg.	Nor.	Nor.		No abnormalities
23	28	multip.	0	3rd mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
24	30	multip. (dystocia)	0	3rd mo.	Neg.	Nor.	Nor.	dyspnea ++, fatigue ++	No abnormalities
27	19	multip.	0	4th mo.	Neg.	Nor.	Nor.		No abnormalities
29	30	primip.	0	4th mo.	Neg.	Nor.	Nor.		No abnormalities

\*Kahn & Wassermann tests.

5. This shifting of the heart produces a left axis deviation in the electrocardiogram of the majority of the patients studied.

6. The normal woman who does not develop any untoward signs or symptoms during the course of pregnancy shows normal clinical, cardio-dynamic, and electrocardiographic findings six to eight weeks after delivery.

Grateful appreciation is acknowledged to the following: John Oldham, for technical assistance, and the American Red Cross, whose aid made this study possible.

#### REFERENCES

1. MacKenzie: Heart Disease and Pregnancy, New York, 1921, Oxford University Press.
2. Jensen, F. G., and Norgaard: Functional Cardiac Disease and Essential Cardiac Hypertrophy in Normal Pregnant Women, *Acta. Obst. et gynec. Scandinav.* 6: 67, 1927.
3. Smith, S. C.: Observation on the Heart in Mothers and Newborn, *J. A. M. A.* 79: 3, 1922.
4. Konki, V.: The Electrocardiogram of the Heart in Pregnancy and Puerperium, *Jap. J. Obst. and Gynec.* 12: 2, 1929.
5. Carr, F. B., and Palmer, R. S.: Observation on Electrocardiography in Heart Disease in Pregnancy With Special Reference to Axis Deviation, *AM. HEART J.* 8: 238, 1932.
6. Carr, F. B., Hamilton, B. E., and Palmer, R.: The Significance of Large Q<sub>s</sub> in Lead III of the Electrocardiogram in Pregnancy, *AM. HEART J.* 8: 519, 1933.
7. Feldman, L., and Hill, Harold H.: The Electrocardiogram of the Normal Heart in Pregnancy, *AM. HEART J.* 10: 110, 1934.
8. Runge, H. R.: *J. A. M. A.* 83: 567, 1924.
9. Spitzer, Walter: Die Blutstromungsgeschwindigkeit in normaler und gestörter Schwangerschaft, *Arch. f. Gynäk.* 154: 449, 1933.
10. Alward, H. C.: The Vital Capacity in the Last Month of Pregnancy. *Am. J. Obst. & Gynec.* 20: 373, 1930.
11. Stander, H. J., and Cadden, J. F.: The Cardiac Output in Pregnant Women, *Am. J. Obst. & Gynec.* 24: 13, 1932.
12. Katz, Louis N., and Landt, Harry: The Effect of Standardized Exercise on the Four-Lead Electrocardiogram, *Am. J. M. Sc.* 189: 346, 1935.
13. Wilson, F. N., Macleod, A. Garrard, and Barker, Paul S.: The Order of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1931-1932.
14. Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R.: Simplified Apparatus for Direct Venous Pressure Determination Modified From Moritz and von Tabora, *Am. J. M. Sc.* 187: 371, 1934.
15. Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R.: Observation on the Practical Significance of Venous Pressure in Health and Disease With a Review of the Literature, *Am. J. M. Sc.* 187: 642, 1934.
16. Hoover, C. F.: Respiratory Excursion of the Thorax, *Oxford Medicine II.* Part I, p. 29.
17. Hynemann—quoted by Konki.<sup>4</sup>
18. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen und den Einfluss der Herzlage auf die Form des Elektrokardiograms, *Arch. f. d. ges. Physiol.* 150: 275, 1913.
19. Cohn, A. E., and Raisbeck, M. T.: The Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9: 311, 1922.

## Department of Clinical Reports

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### IDIOPATHIC HYPERTROPHY OF THE HEART WITH ENDOCARDIAL FIBROSIS\*

REPORT OF TWO CASES

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**I**DIOPATHIC hypertrophy of the myocardium has long been the conventional term for classifying cases of enlargement of the heart in infants and young children for which no clinical or pathological basis could be found.

The idiopathic hypertrophies have their chief clinical features in common, but these features are not absolutely distinctive for the group. Although it has been reported in the newborn and in patients as old as four and one-half years, the average age at recognition is fourteen months. Cases of apparently the same condition have been reported in adults,<sup>19</sup> but it is not yet definitely settled whether these represent an idiopathic hypertrophy which was present since infancy or one which arose later in life. It is usual for the mother's prenatal history and the infant's postnatal history to be negative for infections or other conditions of possible etiological significance, although it is frequently noted that the child was "puny" or developed poorly from time of birth. The onset of heart symptoms is usually rapid and may be attended by fever; so that when the child is first seen, the case is frequently diagnosed as an acute infection, usually pneumonia, less often, pericardial effusion. The course tends rapidly to death, which may occur as quickly as an hour or two after the first symptoms are noticed. The three cardinal findings in these patients are cyanosis, dyspnea, and tachycardia. Moderate anemia has been found when the blood was examined and is now considered part of the clinical picture. Edema and heart murmurs are notably infrequent. It must be emphasized that very frequently physical examination of these patients fails to reveal an enlargement of the heart although the enlargement is shown to be considerable both by x-ray and by autopsy examination. Electrocardiography has not been consistent or informative in the few cases in which it has been done.

Many hypotheses have been offered to explain the condition of "idiopathic hypertrophy of the heart" in infants, but none is yet accepted as satisfactory. The probabilities are that the "idiopathic hypertrophies" do not form a single group; that none of the heart cases are truly idio-

\*From the Department of Pathology, Vanderbilt University Medical School.

pathic; and that eventually they will be subclassified in different etiological subgroups in spite of the clinical features held in common. A start in the subclassification according to etiology has been made by the recognition of glycogenic infiltration of the muscle fibers as the basis for the enlargement in some cases.<sup>14, 15</sup>

Kugel and Stoloff<sup>2</sup> in 1933 reported a thorough search of the literature by which they collected fifty-two previously reported cases of "idiopathic hypertrophy of the heart" in infants. To this number they added seven of their own, the fourth of which had been previously described in a paper by Stoloff.<sup>1</sup> Since the report by Kugel and Stoloff, sixteen more cases have been reported in the available literature. Four were without benefit of autopsy (Filippi<sup>3</sup>; Dufourt<sup>4</sup>; Debré and Broca,<sup>5</sup> second case; Wilkinson,<sup>6</sup> first case); six did not show any changes in the heart associated with the hypertrophy (Wilkinson,<sup>6</sup> second case; Blechman, Deberdt and Azoulay<sup>7</sup>; Ellis<sup>8</sup>; Debré, Marie and Bernard<sup>9</sup>; Debré and Broca,<sup>5</sup> first case; Elizalde<sup>10</sup>); of the remaining six, three showed associated endocardial and myocardial changes (Levine,<sup>11</sup> Kenny and Sanes<sup>12</sup>), one showed coarctation of the aorta alone (Root<sup>13</sup>), and two presented extensive infiltration of the muscle fibers by glycogen (Antopol, Heilbrun and Tuchman<sup>14</sup>; Pompe<sup>15</sup>). It is to be noted that Levine's case<sup>11</sup> presented both endocardial fibrosis and coarctation of the aorta. Of the sixty-three autopsied cases of so-called "idiopathic hypertrophy" reported to date, twenty-two have shown, in addition to the cardiac enlargement, endocardial fibrosis and myocardial degenerative-infiltrative changes, the endocardial and myocardial changes occurring either singly or in combination, and being the "simple cardiac defects" most frequently found associated with the hypertrophy.

In view of the relative rarity of the condition it seems well to report two cases of "idiopathic hypertrophy of the heart" which were encountered within a year's time on the routine autopsy service of Vanderbilt University Hospital.

#### REPORT OF CASES

CASE 1.—The patient, a thirteen-month-old, white female infant, was born normally at full term, free from congenital defects, gained weight, developed normally, and was well until the onset of the present illness seven weeks prior to admission. At that time she contracted a "cold," and several days later had high fever, vomited several times, and seemed quite ill. The local attending physician diagnosed the condition as pneumonia. Her improvement was slow. She continued to breathe fast and to be very restless, but took her feedings well. During the period of improvement she coughed a great deal and vomited occasionally, but no fever was noted. Three days prior to admission there developed generalized edema and some swelling of the abdomen, oliguria, and occasional attacks of cyanosis. On admission the temperature was 101° F., pulse 144, respiration 74, and blood pressure 100/80.

Examination revealed a thirteen-month-old, white female infant acutely ill. There was generalized edema, including the face and hands. The nail beds were cyanotic,

respiration rapid and labored. The neck veins were distended, and the peripheral pulse was feeble. Physical examination and x-ray film of the chest revealed enlargement of the heart to the left, and other signs suggested pericardial effusion. Examination of the lungs revealed nothing remarkable. The liver was enlarged nearly to the umbilicus; the spleen was palpable.

On the strength of the physical findings and the x-ray confirmation, an attempt was made to tap the pericardium. There was obtained 1 c.c. of bloody fluid followed by  $\frac{7}{8}$  c.c. of light straw-colored fluid. The heart was then felt beating against the point of the needle and the procedure was discontinued. In the late afternoon of the second day, after thirty-six hours of extreme oliguria, she was given 40 c.c. of 30 per cent glucose solution intravenously, and subsequently voided fairly large amounts of urine, and the generalized edema diminished noticeably. Her respiratory distress, however, grew increasingly severe in spite of oxygen tent and stimulants; the temperature rose to 105-106° F.; and on the morning of the third day in the hospital the lungs filled with moisture, and the patient died.

Urinalysis showed albumin, a few hyaline and cellular casts, and many colon bacilli. The red blood cell count was 3,740,000 with 10 gm. of hemoglobin. The total white count was 9,750 with 72 per cent polymorphonuclears. The blood Wassermann test was negative. The blood culture was sterile. The total serum protein was 5.26, with albumin 3.3, and globulin 1.96.

*Post-mortem examination* was done one hour after death. There were moderate dependent edema, ascites, enlargement of the liver, massive edema of the mesentery and retroperitoneal tissues, and moderate bilateral hydrothorax. The pericardial cavity contained from 50 to 60 c.c. of bloody fluid, and an area of subepicardial hemorrhage was found on the anterior surface near the apex.

The heart was greatly enlarged (Fig. 1), extending from a point 2-3 cm. on the right of the midline almost to the left chest wall. It lay in a transverse plane, and all the chambers were dilated. The foramen ovale and the ductus arteriosus were completely obliterated. The aorta was normal, and it was noted that there was no stenosis of the aorta at any point. The great vessels entered and left the heart normally. Both right auricle and ventricle were dilated, and the interventricular septum bulged into the cavity of the right ventricle. The endocardium on the right side was normal in appearance. The left auricle and ventricle were dilated, and the endocardium in each chamber was uniformly thickened and grayish white (Fig. 1). The free margins of the mitral and tricuspid valves showed slight to moderate fibrous thickening, and the major portion of the valves was thickened generally. The chordae tendineae were thickened and shortened, and the papillary muscles were shortened. The septum was intact. The aortic valve was normal.

The lungs and the liver showed evidence of chronic passive congestion. The other organs were not remarkable.

*Microscopic Examination.—Heart:* The endocardium of the left auricle and ventricle showed marked irregular fibroelastic thickening, the most of the tissue being elastic. The elastic fibers were largest and most compactly arranged in the deeper layers, while toward the surface they became thinner and separated by increasing quantities of finely fibrillar collagenous material. No inflammatory cells were found in the endocardium. Irregular projections of fibrous tissue entered the underlying myocardium and surrounded or replaced large areas of muscle tissue. These areas of fibrosis, too, contained large proportions of elastic tissue. There was marked periarterial fibrosis.

The muscle fibers were not noticeably hypertrophied but showed very marked thinning throughout large areas, especially in the wall of the dilated left ventricle. Some granular changes were present in the muscle fibers, but there was no vacuolation except for an accentuation of the normal vacuolation in the Purkinje fibers. Fat could not be demonstrated, and there was nothing to suggest glycogen infiltra-

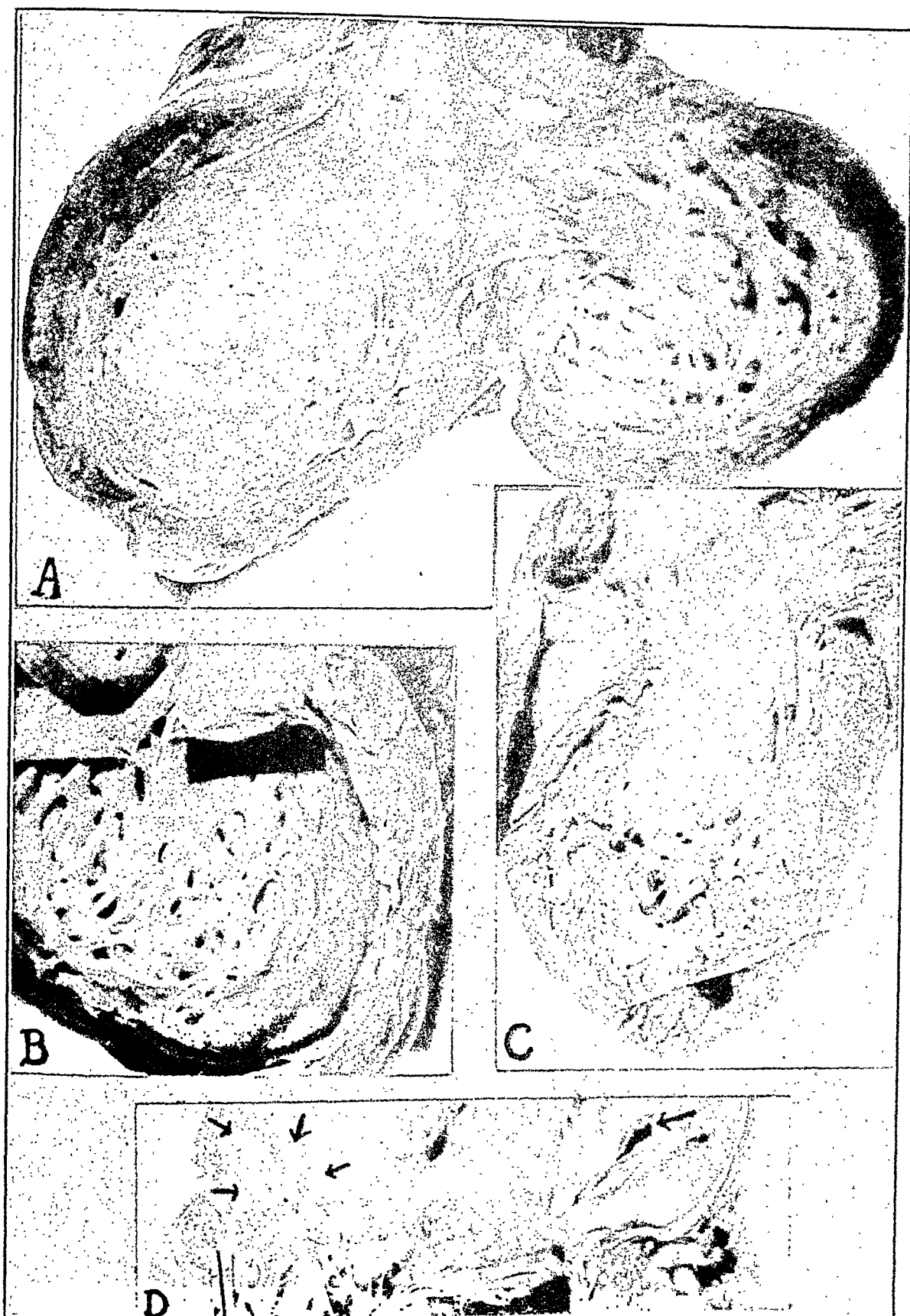


Fig. 1.—A (Case 1), left ventricular hypertrophy, dilatation, and endocardial fibrosis. B (Case 1), left ventricle and mitral valve. C (Case 2), left ventricular hypertrophy and endocardial fibrosis. D (Case 2), mitral valve; foramen ovale (arrow) and plaque on wall of left auricle (arrows). The posterior cusp of the mitral valve is seen below the mural plaque.



tion of the fibers. There were many extensive areas of excessive thinning, granular degeneration, and disappearance of the muscle fibers. The interstitial spaces in such areas were filled with fine collagen fibrils and were heavily infiltrated by round cells. Dense collections of large and small round cells were found along the veins but not the arteries. No Aschoff bodies were seen (Fig. 2).

Sections were taken from the right circumflex, left circumflex, left anterior descending, and descending branches of the left circumflex coronary arteries, and studied with hematoxylin eosin, Mallory's aniline blue stain, and Weigert's elastic tissue stain. Their structure conformed closely to the normal for this age group as described by Gross, Epstein, and Kugel.<sup>17</sup>

The lungs and liver presented microscopic evidence of chronic passive congestion, and, in addition, the liver showed massive midzonal hemorrhages and vacuolar and hyaline degeneration of the parenchymatous cells. There was acute splenitis and acute lymphadenitis.

CASE 2.—The patient was a two-and-one-half-year-old white male, who entered the hospital for the first time Feb. 3, 1935, with the chief complaint of asthma. He had always been a "puny" child, and at the age of five months had an attack of pneumonia. The local attending physician at this time said he had a heart murmur which had probably been there since birth. When the child was about eighteen months old, he began to have wheezing attacks. These were characterized by easy inspiration and difficult expiration, and they continued all winter. One such attack was said to have been relieved almost immediately by an injection of adrenalin. With the coming of spring the asthma was almost completely relieved but recurred again in December and persisted to the time of admission. The wheezing now was worse in the middle of the day, less at night or during periods of relaxation, and there was no notable increase in connection with exercise. No cyanosis or dyspnea had been noted. A week before first admission puffiness of the face was noticed, and four days later his face and feet were greatly swollen. There was no past history of rheumatic diatheses. The family history was positive for allergy. His diet had always consisted chiefly of milk.

*Examination* showed an acutely ill, undernourished, young white boy slightly cyanotic, dyspneic and orthopneic, and generally edematous. There was moderate distention of the neck veins. Physical examination, confirmed by x-ray and fluoroscopy, showed the heart to be markedly enlarged, with pulsations indistinct, but no change in contour with change of position. The rhythm was regular, rate 140, blood pressure 115/82. The sounds were faint, and a soft blowing systolic murmur was heard over the precordium. Electrocardiography showed only sinus tachycardia. The liver was markedly distended; the spleen was not palpable. The child was given extreme measures—oxygen tent, diuretics, stimulants, digitalis—and responded well.

Skin tests showed him to be sensitive to milk, which had been almost his sole article of diet. Blood tests showed a moderate anemia: 3.8 million red cells and 8.5 grams hemoglobin. In accordance with all these findings it was concluded that the condition was entirely due to allergic asthma and nutritional anemia with low serum proteins, all of which had combined to produce cardiac hypertrophy, dilatation, and decompensation. He was accordingly treated by desensitization, proper diet, and whole blood intravenously. There was marked improvement. At time of discharge he wheezed only a little; the heart had decreased in size to within the nipple line; the systolic murmur was still heard, best at the mitral area; and the liver had receded to the costal margin. His enlarged adenoids had been removed during his stay in the hospital.

Three months later he was readmitted. His interval history was that he had done fairly well, though continuing to have some respiratory difficulty. He

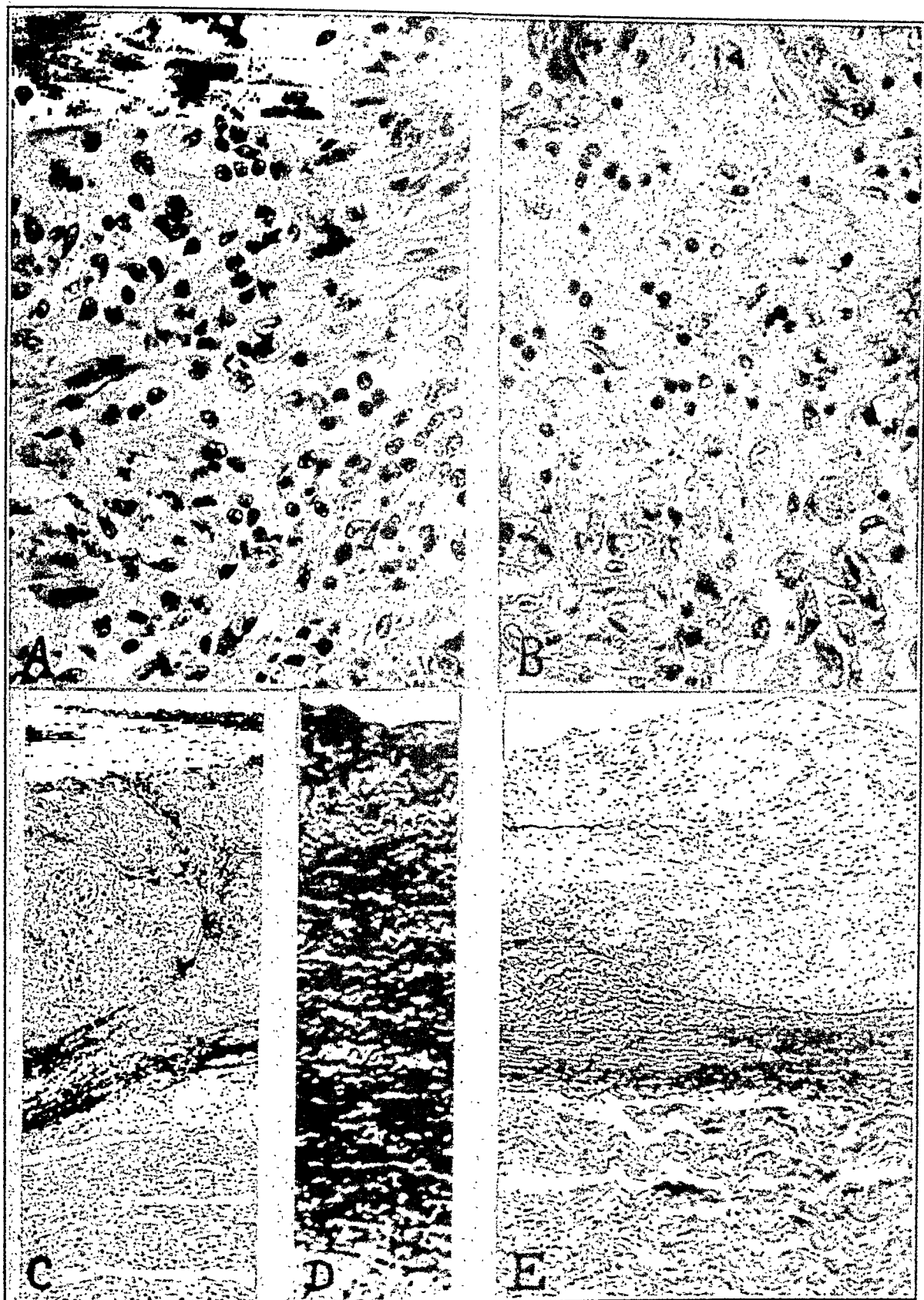


Fig. 2.—A (Case 1), myocardial degeneration and infiltration,  $\times 450$ . B (Case 2), myocardial degeneration and infiltration. C (Case 1), elastic thickening of left ventricular endocardium. Weigert's elastic stain,  $\times 55$ . D the same,  $\times 280$ . E (Case 2), plaque on wall of left auricle. Weigert's elastic tissue stain,  $\times 55$ .

returned to the hospital only as a precautionary measure. On this admission the temperature was 98.8° F.; pulse, 120; respiration, 32; and blood pressure, 100/76. The child was not acutely ill. There was no cyanosis, and there was no edema, dependent or otherwise. He breathed with a wheeze and had an occasional cough. Epigastric pulsation was seen. Examination of the heart was the same as on the first admission. The lungs showed some râles, bubbles, and squeaks. The liver was enlarged three fingerbreadths below the costal margin.

The child appeared to be doing well until on the sixth day of hospitalization he suddenly began to have respiratory distress attended with pallor. This increased in spite of all measures including the oxygen tent; acute pulmonary edema developed and became increasingly worse until death supervened some five to six hours after the unexpected onset of acute symptoms.

The blood Wassermann and Kahn tests were negative. The total red blood cell count was 4.2 million; the total white count 9,150 with 55 per cent polymorphonuclears. Total blood serum proteins were 5.82, with albumin 4.3, and globulin 1.52. Routine urinalysis was normal.

*Autopsy* was performed four and a half hours post-mortem. There was no edema. The serous cavities contained no free fluid.

The *heart* (Fig. 1) weighed 150 gm. Normal weight for a child of this age is 58 gm.<sup>16</sup> Both ventricles were dilated and hypertrophied, the right proportionately more than the left. The wall of the right ventricle was 9 mm. thick, that of the left 1.5 cm. The epicardium was clear and glistening. The entire endocardium showed a diffuse fibrosis most marked in the two left chambers. The myocardium was markedly pale, gray, and flabby. The entire border of the mitral valve was rolled and thickened by confluent, translucent, pink nodules. There was some diffuse fibrosis of the entire valve, but no fibrosis of the chordae tendineae. The border of the posterior cusp of the mitral valve was especially involved, and there was apparently a considerable shortening of the cusp which measured only 3-5 mm. between free and attached borders. Extending up from this cusp onto the wall of the left auricle, covering an area about 1 × 1.5 cm. in size, was a raised irregular patch of the same type of pink translucent tissue found along the border of the mitral valve. The tricuspid valve showed similar nodules along its free border with involvement of a considerable part of one cusp. The main part of the tricuspid valve, however, was thin and translucent; there was little distortion and no diminution in the size of the valve; and there was no fibrosis of the chordae tendineae. These lesions of the mitral and tricuspid valves grossly resembled those of rheumatic fever but were not absolutely typical. The aortic and pulmonic valves were normal. The interauricular septum presented a circular opening 6 mm. in diameter, the rim of which was thick and fibrous and presented many small nodules of the type seen on the mitral and tricuspid valves. Further examination revealed what appeared to be the line of original fusion of the foramen ovale, and it was judged that the opening had resulted from erosion by a process similar to that involving the atrioventricular valves and the wall of the left auricle. The aorta was normal. The large vessels opened into the heart normally. The ductus arteriosus was closed.

The left lung was compressed to almost half the size of the right. The lungs were dense, dark red on section, and very edematous. The gastrointestinal tract was not remarkable. The liver weighed 450 gm., which is normal for a child of this age,<sup>16</sup> and showed no gross evidence of chronic passive congestion. The spleen weighed 80 gm., about twice normal weight, and was very firm. There were no other remarkable features in the gross findings.

*Microscopic Examination.*—*Heart* (Fig. 2): The endocardium of all the chambers showed marked fibroelastic hyperplasia, quite irregular in thickness and frequently

extending deep into the myocardium to surround or replace large areas of muscle fibers. This fibrous tissue was composed of elastic and collagenous elements in the same proportions and arrangement as described for the first case. Section of the mitral valve, posterior cusp, and the plaque above it on the wall of the left auricle showed massive and irregular fibrosis of the valve with only a few bundles of fine elastic fibers. There were no inflammatory cells, vessel changes, or other signs of active inflammation in the valve. The plaque on the left auricular wall was composed of two layers—a superficial layer of very edematous fibrous tissue, rich in plump fibroblastic nuclei, lacking any infiltration of inflammatory cells, and showing only a few fine, irregularly disposed elastic fibers. A deeper layer consisted of adult fibrous tissue, chiefly elastic, in compact parallel bundles.

The coronary system was studied as in the first case and likewise was found to be essentially normal.

The perivascular fibrous tissue was much increased. The interstitial tissue as a rule was only slightly increased in amount, but there were many foci in which there was marked interstitial fibrosis of the same composition noted in the endocardium. The muscle fibers did not appear hypertrophic but rather attenuated and distorted. No fat could be demonstrated. There was no vacuolation or other findings suggestive of glycogen in the fibers. There were some areas in which the muscle fibers had disappeared altogether, and there remained only a fine endomysial network within which were many fibroblasts and infiltrating round cells. The capillaries of these areas showed marked swelling and proliferation of the endothelial cells which frequently formed a layer two to four cells thick. A moderate degree of interstitial round cell infiltration was seen in many areas other than those just noted. Occasional interstitial hemorrhage was seen.

The lungs presented microscopic evidence of chronic passive congestion. There was no hypertrophy of the bronchial musculature, eosinophilic infiltrations, or other findings considered indicative of bronchial asthma. A bronchial lymph node contained a well walled-off caseous tubercle. Microscopic examination of the other organs was not remarkable.

#### DISCUSSION

In both of the cases here reported there was a history of good health from birth to the time of an illness which was diagnosed pneumonia, after which symptoms of heart failure appeared and grew worse to the time of death. It might be interpreted here, as elsewhere,<sup>12</sup> that the sequence was: respiratory infection; toxic myocarditis with degeneration, fibrous repair, dilatation of the surviving muscle fibers; and finally a compensatory hypertrophy. However, the anatomical evidence would indicate that the hypertrophy and the endocardial fibrosis were older than the degenerative-infiltrative process in the myocardium, and, in the first case particularly, seem much older than would be compatible with the relatively short time between "pneumonia" and death. It seems more probable<sup>18</sup> that, granting an acute infection antecedent to the heart failure, the heart was damaged by the infection because it was already in a pathological condition (hypertrophy and endocardial fibrosis) and was susceptible to fatal damage by a minor intoxication that would not have affected a normal heart.

Definite allergy to milk, which had been the main article of diet throughout the patient's life, was a prominent feature of the second

case. The asthma was explained on this basis before death though considerable doubt was raised about the correctness of this explanation when autopsy showed the type of heart that was present. The asthma, in turn, could explain the right-sided hypertrophy and dilatation but could hardly serve as a basis for the left-sided hypertrophy and myocardial-endocardial changes. In view of the resemblance of the lesions on the mitral valve and wall of the left auricle to similarly located lesions in rheumatic fever, the question was raised whether food allergy might not have produced these endocardial lesions by a mechanism analogous to that supposed by some<sup>20, 21</sup> to operate in rheumatic fever. However, there is no clinical or experimental evidence yet to support the idea that food allergy may cause anatomical heart lesions.

Endocardial fibrosis was in these two cases a feature of the heart second in prominence only to the hypertrophy of the myocardium. The associated lesions of the heart valves and, in the second case, of the left auricular endocardium, suggest an inflammatory origin for at least a part of the fibrosis in these cases.

A micrometer was used to compare the size of the individual myocardial fibers in the two cases just reported and in other cases of the same ages free from enlargement or other pathological condition of the heart. This comparison confirmed the original impression that the diameter of the heart fibers was not enlarged and showed that on an average the fibers were thinner than those in the supposedly "normal" hearts. This raised the question of how to explain the marked enlargement of the heart in both cases just reported, and whether it might be explained on the basis of hyperplasia of the fiber bundles rather than of hypertrophy of the individual fibers.

#### SUMMARY

Two new cases of idiopathic myocardial hypertrophy of infancy are reported. Both cases conformed fairly well to the clinical course which has been recognized as generally occurring in cases of idiopathic hypertrophy, although each had the unusual clinical history of antecedent infection and each presented edema when first seen. Both cases showed fibroelastic thickening of the endocardium, myocardial hypertrophy and dilatation, and microscopic degeneration, round cell infiltration, and fibrosis of the heart muscle. In addition, the second case presented food allergy and asthma, presumably allergic, and on autopsy showed lesions resembling those of rheumatic fever on the mitral valve and wall of left auricle.

Antecedent acute infection was considered insufficient to explain the heart changes in these two cases. The history of such infections has been questionable in the majority of cases in which it has been reported; and

it seemed probable that, even when definitely present, the infection was of importance rather for precipitating the acute decompensation than for producing the hypertrophy.

The question was raised whether food allergy may have been responsible for the rheumatoid lesions in the left heart of the second case, and whether the allergic factor is ever present in other cases as an etiologic factor.

No conclusions were reached as to the etiology of the endocardial and myocardial changes in the two cases reported.

#### REFERENCES

1. Stoloff, E. G.: *Am. J. Dis. Child.* 36: 1204, 1928.
2. Kugel, M. A., and Stoloff, E. G.: *Am. J. Dis. Child.* 45: 828, 1933.
3. Filippi, Felipe de.: *Arch. argent. de pediat.* 3: 773, 1932.
4. Dufourt, André: *J. de méd. de Lyon* 14: 127, 1933.
5. Debré, R., and Broca, R.: *Bull. méd., Paris* 48: 311, 1934.
6. Wilkinson, S. J.: *Radiol. Rev. & Chicago M. Rec.* 54: 284, 1932.
7. Blechman, Deberdt, and Azoulay: *Arch. de méd. d. enf.* 37: 154, 1934.
8. Ellis, R. W. B.: *Proc. Roy. Soc. Med.* 28: 1330, 1935.
9. Debré, Marie, and Bernard: *Bull. et mém. Soc. méd. d. hôp. de Paris* 51: 995, 1935.
10. Elizalde, P. de: *Arch. argent. de pediat.* 4: 88, 1933.
11. Levine, H. D.: *Am. J. Dis. Child.* 48: 1072, 1934.
12. Kenny, F. E., and Sanes, S.: *J. Pediat.* 3: 321, 1933.
13. Root, J. H.: *Arch. Pediat.* 50: 414, 1933.
14. Antopol, Heilbrun, and Tuchman: *Am. J. M. Sc.* 188: 354, 1934.
15. Pompe, J. C.: *Ann. d'anat. Path.* 10: 23, 1933.
16. Bovaird and Nicoll: *Arch. Pediat.* 23: 641, 1906.
17. Gross, L., Epstein, E. Z., and Kugel, M. A.: *Am. J. Path.* 10: 253, 1934.
18. Goodpasture, E. W.: Personal communication.
19. Levy, R. L., and Rousselot, L. M.: *AM. HEART J.* 9: 178, 1933.
20. Swift, H. F., et al.: *Tr. A. Am. Physicians* 43: 192, 1928; *J. A. M. A.* 92: 2071, 1929; *AM. HEART J.* 6: 625, 1931.
21. Moon, V. H., and Stewart, H. L.: *Arch. of Path.* 11: 190, 1931.

## CARDIAC ASTHMA DUE TO OCCLUDING THROMBUS OF THE LEFT AURICLE\*

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CARDIAC asthma usually is due to failure of the left ventricle, which has been damaged previously as the result of hypertension, coronary artery sclerosis, or aortic valve disease. In a small group of cases, however, the same type of paroxysmal dyspnea results from the presence of mitral stenosis without myocardial failure. A series of cases of the latter type has been studied by McGinn and White,<sup>1</sup> who point out that in this group the attacks usually are precipitated by exertion, emotional upsets, or paroxysmal tachycardia. When the heart rate is accelerated by any of these factors, blood is expelled into the pulmonary circulation by the hypertrophied right ventricle more rapidly than it can pass through the narrowed mitral orifice. The resulting acute pulmonary hypertension and congestion causes paroxysmal dyspnea which may be accompanied by asthmatic breathing and may progress to acute pulmonary edema.

In the present communication we wish to report a case of mitral stenosis and subacute bacterial endocarditis in which an occluding thrombus of the left auricle was responsible for a typical attack of cardiac asthma.

### REPORT OF CASE

*History.*—A white male office worker, aged forty-six years, was brought to the hospital by ambulance on March 10, 1936. Approximately four months earlier, he had noted the onset of anorexia and increasing tendency to fatigue, periodic vague distress in the epigastrium and left upper quadrant of the abdomen, and dyspnea and palpitation on exertion. Several weeks after the appearance of these symptoms, an irritating, slightly productive cough had developed. The patient continued to work until February 8, when he was forced to quit because of dyspnea, weakness, and feverishness. At this time the presence of irregular, low grade fever was discovered. During the month before admission to the hospital, there had been frequent attacks of severe retching, and on a few occasions the patient had vomited a small amount of bile-stained material. At times these attacks had been precipitated by a sudden change in position and particularly by sitting up in bed. During the three weeks preceding admission, the patient also had experienced three attacks of severe paroxysmal dyspnea which were not accompanied by wheezing. He had felt compelled to sit up in bed during the seizures but, on doing so in the first two paroxysms, had promptly lost consciousness. None of the attacks had lasted for more than fifteen minutes. There had been a loss of fifteen pounds in weight since the onset of the illness.

*Examination.*—The patient was well developed and well nourished but appeared to be quite ill. The skin had a light yellowish tint, and the sclerae showed

\*From the Cleveland Clinic.

slight but definite icterus. The pupils reacted normally. The jugular veins were not distended. Relative cardiac dullness extended 1 cm. beyond the left mid-clavicular line in the fifth interspace. The heart rhythm was regular, and the rate was 112 per minute. Over the apex a rumbling murmur was heard beginning early in diastole and extending up to a loud first sound. No other murmurs were present. The pulmonary second sound was louder than the aortic second but was not definitely accentuated. A few medium moist râles were present over the base of both lungs. The liver and spleen could not be felt. There was no clubbing of the fingers, and no petechiae were seen. The arterial blood pressure was 120 mm. systolic and 70 mm. diastolic. The temperature by mouth was 98.4° F.

The red blood cell count was 5,160,000 per cubic millimeter, and the hemoglobin content, 91 per cent. The leucocyte count was 17,600 per cubic millimeter. The urine contained a trace of albumin, many hyaline and finely granular casts,

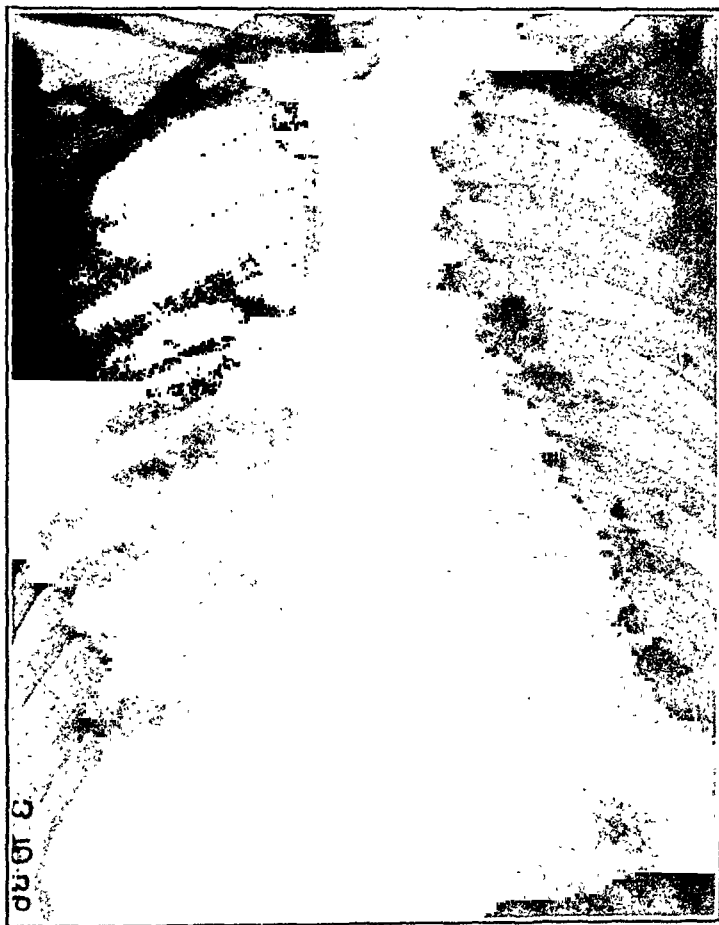


Fig. 1.—Roentgenogram of the chest showing increased hilus shadows with fanlike radiation toward the periphery.

and an occasional red blood cell. The Wassermann and Kahn reactions of the blood were negative. The icteric index was 25. A blood culture gave a growth of nonhemolytic streptococci at the end of sixty hours.

Roentgenograms of the chest (Fig. 1) showed moderate enlargement of the heart, with prominence of the curve due to the pulmonary conus and left auricular appendage. In addition, the lung hilus shadows were greatly increased in width, with extensive fanlike radiation toward the periphery. In the region of the aortic arch, a rather large area of increased density also was present, the nature of which was not clear.

An electrocardiogram showed sinus tachycardia, with a rate of 110 per minute. The maximum amplitude of the QRS complexes was 4 mm. in Lead II. The P-waves were prominent in Leads I and II and the T-waves were isoelectric in all leads.



*Clinical Course.*—Several hours after admission to the hospital, and while he was lying quietly in bed, the patient suddenly began to experience intense dyspnea. At the same time the lips and nail beds became cyanotic and the face very pale. Profuse perspiration developed, and the hands, forearms, feet, and legs became cold and clammy. The dyspnea increased rapidly in severity so that the accessory muscles of respiration were brought into play, and within a few minutes the breathing became asthmatic in type with loud wheezing, especially during expiration. In spite of the great respiratory difficulty, however, the patient declined to be elevated to a sitting position. Rhonchi were first noted over the upper left anterior chest a few minutes after the onset of the paroxysm. These increased rapidly in numbers and were soon present over all lung fields. Frequent coughing developed early in the attack and was productive of small amounts of thick tenacious sputum flecked with blood. Shortly before the onset of the paroxysm, the pulse rate had been 128 per minute, but the development of dyspnea was attended by a rapid rise



Fig. 2.—Photograph of interior of left auricle showing mitral valve orifice almost completely obstructed by the large vegetative thrombus.

to 140 and then to 154 per minute. The cardiac rhythm remained regular. A decrease in blood pressure to 100 systolic and 70 diastolic was recorded. One-fourth grain of morphine sulphate was administered hypodermically and resulted in gradual, but only partial, relief. One hour after the first appearance of symptoms, moderate dyspnea and wheezing still were present, and sibilant râles were to be heard throughout all lung fields although in diminished numbers. Intermittent cough persisted, and the sputum at this time was bright red in color. The administration of morphine sulphate was repeated, and one hour later the patient was much more comfortable. Numerous rhonchi were still present over the left lung; profuse sweating continued; the nail beds and the lips were deeply cyanotic; and the extremities remained cold and clammy. The pulse rate was 152 per minute; the blood pressure, 85 mm. systolic and 60 mm. diastolic; and the temperature, 103.8° F. The radial pulse wave was barely palpable.

On the following morning, the patient, although comfortable, still appeared to be critically ill. The lips and nail beds remained cyanotic, and the jugular veins were moderately distended. The extremities were cold and clammy. The radial pulse at times could not be felt. The blood pressure was 80 systolic; a diastolic reading could not be obtained. The heart sounds were of good quality, but the diastolic murmur over the apex was less well heard than formerly. The cardiac rate was 96 per minute, and the rhythm was regular. A moderate number of medium râles were present over the bases of both lungs. The liver edge was not palpable. During the latter part of the night, large amounts of greenish fluid had been vomited on four occasions.

Throughout the day the patient's condition remained essentially unchanged except for occasional periods of nausea and a gradual further decrease in blood pressure to 60 systolic. This low level was maintained subsequently with but

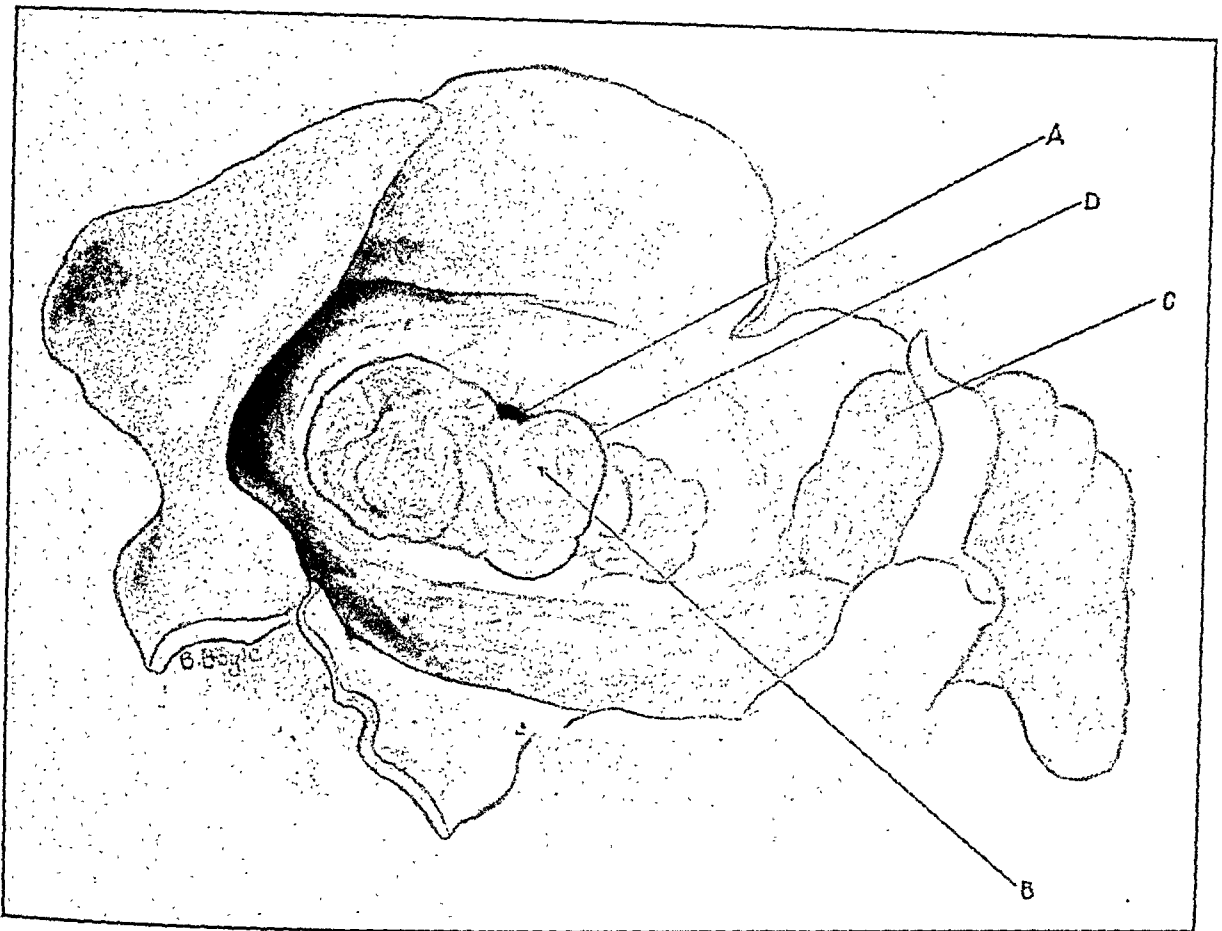


Fig. 3.—Drawing of interior of left auricle. A, unobstructed portion of mitral valve orifice. B, free portion of vegetative thrombus overlying the mitral valve orifice. The lateral border of the thrombus is indicated by the heavy line. C, ante-mortem thrombus in left auricular appendage. D, region of the small area of secondary attachment of the thrombus on its posteroinferior border. The angle of view of the drawing is slightly different from that in the photograph (Fig. 2).

slight variations except for a rise to 76 for a few hours on the morning of the second day after admission. This rise seemed to be accompanied by temporary, slight improvement in the temperature of the legs. The output of urine amounted to 240 c.c. during the first twenty-four hours in the hospital and to but 80 c.c. during the second twenty-four hours. Death occurred on the morning of the third day after admission. The patient remained clear mentally and experienced very little further dyspnea until eight hours before he expired. No petechiae were noted at any time, and no gangrenous areas developed in the extremities.

*Post-Mortem Examination.*—At necropsy the right pleural cavity contained 1,400 c.c. of clear, straw-colored fluid, and the left pleural cavity, 1,200 c.c. The peri-

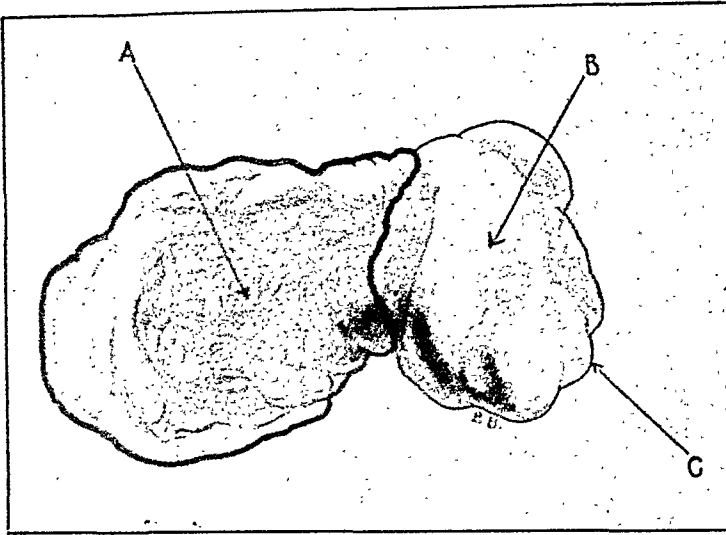


Fig. 4.—Inferior view of the thrombus after its removal. The area of attachment, *A*, has been outlined with a heavy line. The free portion is indicated by *B*, and *C* is directed toward the small area of secondary attachment.

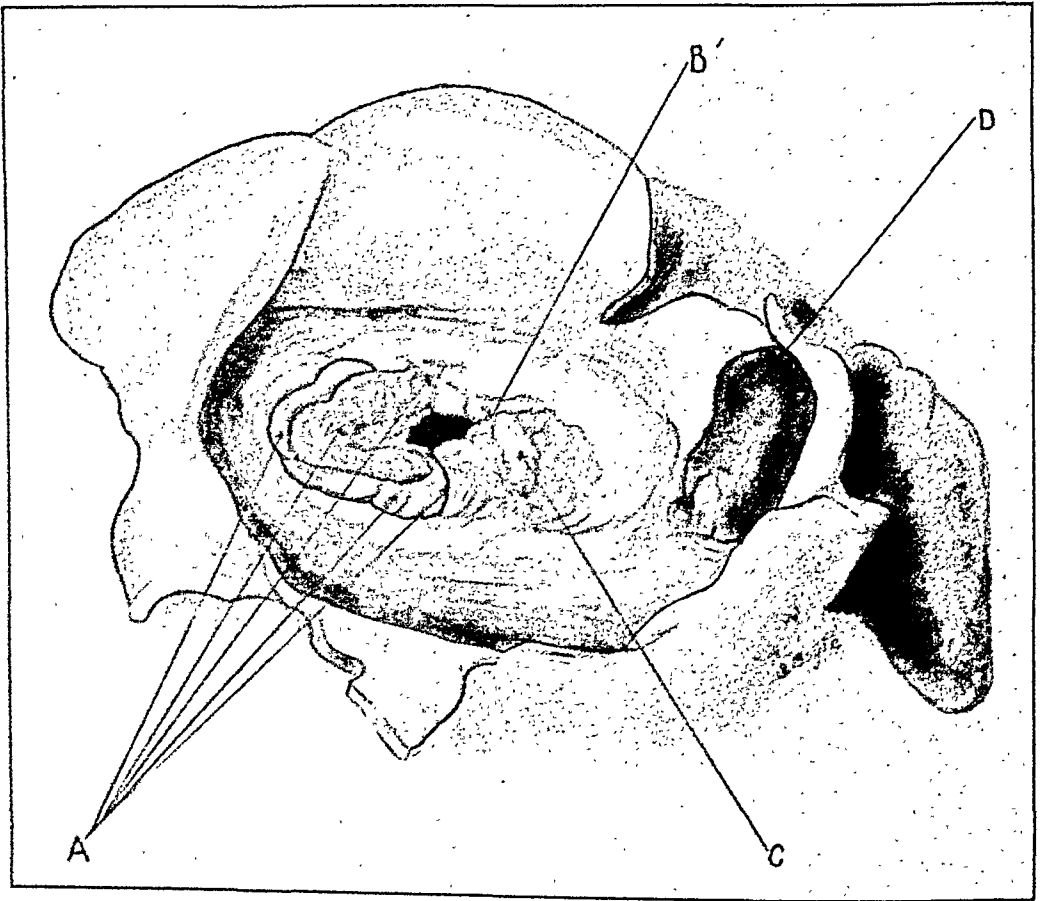


Fig. 5.—Interior of left auricle after removal of the thrombus. *A*, area of attachment of the thrombus. *B*, small area of secondary attachment. *C*, vegetative material not attached to thrombus. *D*, ante-mortem thrombus in left auricular appendage.

cardial sac contained 15 c.c. of clear fluid. A few fresh, fibrinous adhesions were present between the parietal and visceral pericardium over the pulmonary conus. The superior vena cava and the innominate veins were greatly engorged with blood. There were no masses in the mediastinum.

The heart weighed 520 gm. The left auricle, the pulmonary veins, and the right chambers of the heart were greatly dilated and distended with blood. The left ventricle, in contrast, appeared relatively small. The wall of the left ventricle measured 19 mm. at its point of greatest thickness, and the right ventricle 8 mm.

The mitral valve orifice, when viewed from above, was almost completely obstructed by a large, friable, rough, pinkish gray vegetative thrombus which originated from the medial half of the fused leaflets of the valve (Figs. 2 and 3). This thrombus measured 27 mm. in length, 9 mm. in breadth and 3 to 7 mm. in thickness. The medial two-thirds (Fig. 4) was uniformly attached to the underlying structures, but the thicker, lateral one-third was free except for a small area measuring 1 by 3 mm. on the posteroinferior border near the lateral extremity. This latter area was loosely adherent to underlying vegetative material. The free portion of the thrombus completely overlapped the mitral valve orifice except for an area 2 by 3 mm. adjacent to the middle of the posterior leaflet of the valve. In this area there was an indentation in the thrombus, but even here the passage to the left ventricle was not wholly direct since the valve leaflet sloped downward and forward to form a tunnel under the thrombus. A slight degree of free movement was present in the free portion of the thrombus.

After removing the thrombus, a flat, rough vegetative lesion was found completely surrounding the mitral valve orifice except for an area 4 mm. in length on the posterior leaflet (Fig. 5). The valve orifice itself measured 4 mm. by 7 mm. in its greatest diameter. The free margins of the leaflets were firm and greatly thickened. The appendage of the left auricle was filled with an ante-mortem thrombus of recent origin.

The ventricular surface of the mitral valve was free from vegetations. The chordae tendineae were greatly thickened and shortened. The tricuspid, the aortic, and the pulmonary valve leaflets were normal. The tricuspid valve ring measured 11 cm. in circumference, the aortic, 8.3 cm., and the pulmonary, 8.7 cm.

The lungs showed extensive passive congestion. The liver was congested and weighed 1,830 gm. The spleen weighed 490 gm. and contained several old and recent areas of infarction measuring up to 1.5 cm. in diameter. Multiple small infarcts also were found in both kidneys.

#### DISCUSSION

Occluding thrombi of the left auricle usually are associated with mitral stenosis and auricular fibrillation. Instances have been recorded, however, in which auricular fibrillation has been present without mitral stenosis,<sup>2</sup> and in a few cases,<sup>3</sup> as in ours, the occluding thrombus has resulted from bacterial endocarditis in patients with mitral stenosis and regular rhythm. Regardless of the underlying cause, the most important clinical feature of the condition consists of sudden temporary or permanent changes in the peripheral circulation due to an increase in the degree of occlusion of the mitral valve orifice. These changes consist of diminution or disappearance of the arterial pulsations in the arms and legs, extreme coldness of the extremities, cyanosis, and diminished arterial blood pressure. Circumscribed gangrene may develop in the finger tips, toes, or tip of the nose.

Cardiac asthma has been noted but rarely in the recorded cases of occluding thrombi of the left auricle. Schwartz and Biloon,<sup>4</sup> however, mention the occurrence of paroxysmal dyspnea in two of their three patients, and in one of these wheezing was present and blood tinged sputum was expectorated. In the presence of occluding thrombi, cardiac asthma might be expected to result from either of two mechanisms which would produce acute pulmonary congestion: (1) a rapid rise in heart rate, the factor responsible for the development of cardiac asthma in patients with uncomplicated mitral stenosis,<sup>1</sup> and (2) a sudden increase in the degree of occlusion of the mitral valve orifice due to a change in the position of the thrombus. In our patient, the tachycardia which accompanied the onset of the attack can reasonably be assumed to have been of importance in producing the paroxysm. The diminution in the arterial pulsations in the extremities, the coldness of the forearms, the hands, the legs, and the feet, and the decrease in arterial blood pressure, together with the fact that these changes persisted after the attack had subsided, indicate, however, that an increase in the degree of occlusion of the mitral valve also played an important rôle. No conclusion can be drawn as to which of the two mechanisms was the principal cause of the actual initiation of the seizure.

The three attacks of paroxysmal dyspnea experienced by the patient before admission to the hospital probably were the result of the same changes which produced the paroxysm while he was in the hospital. Whether the syncope which occurred in two of the attacks when the patient sat up was the result of the already greatly impaired peripheral circulation or was due to a further increase in the degree of mitral valve obstruction through the effect of gravity upon the thrombus cannot be stated. The patient's refusal to sit up during the attack in the hospital was in striking contrast to his severe dyspnea.

#### SUMMARY

Clinical and post-mortem observations are presented on a patient with advanced mitral stenosis, regular heart rhythm, subacute bacterial endocarditis, and an occluding thrombus of the left auricle. The striking clinical feature was the occurrence of an attack of typical cardiac asthma accompanied by tachycardia and signs of greatly impaired peripheral circulation. The latter signs persisted after subsidence of the paroxysmal dyspnea and tachycardia.

#### REFERENCES

1. McGinn, S., and White, P. D.: Acute Pulmonary Congestion and Cardiac Asthma in Patients With Mitral Stenosis, *AM. HEART J.* 9: 697, 1934.
2. Kaplan, D., and Hollingsworth, E. W.: Pedunculated Thrombus of the Left Auricle Stimulating Mitral Stenosis, *J. A. M. A.* 105: 1264, 1935.
3. Schiller, I. A.: Bacterial Endocarditis With Clinical Picture of "Ball-Valve Thrombus" of the Left Auricle, *J. Mt. Sinai Hosp.* 2: 153, 1935.
4. Schwartz, S. P., and Biloon, S.: Clinical Signs of Occluding Thrombi of the Left Auricle, *AM. HEART J.* 7: 84, 1931.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Chillingworth, Flex P., Sweet, Marian H., and Healy, James C.: Vascular Injection as Influenced by Negative Pressure. *Anat. Rec.* 66: 113, 1936.

When an animal is chloroformed to death, an injection cannula inserted into the left ventricle, and the animal exposed to a negative pressure of 25 to 60 mm. Hg, injection fluid at atmospheric pressure flows in to fill the vascular system more completely than when the animal is at atmospheric pressure and the fluid under high positive pressure. By this new method 60 per cent more fluid can be injected, and minute vessel structure is more clearly outlined.

AUTHOR.

Hopf, E.: A New Electrical Method of Plethysmography in Man. *Ztschr. f. Kreislaufforsch.* 28: 318, 1936.

The method which the author used to register arm volume is sensitive enough to pick up changes in volume of 0.03 to 0.04 c.c. It registers the changes in volume during respiration and during the heart cycle.

The method consists of a "beat circuit" in which changes in "beat tone" are produced by alterations in the condenser field caused by volume changes of the arm. The alterations in pitch can be magnified to be heard in a loud-speaker or can be recorded with an oscillograph. These can be rectified with an anode rectifier and then, after amplification, can be recorded with an oscillograph as intensity changes.

L. N. K.

Gilson, A. S., Jr.: The Effects Upon the Heart Rhythm of Premature Stimuli Applied to the Pacemaker and to the Atrium. *Am. J. Physiol.* 116: 358, 1936.

Using electrograms recorded from the sinus and from the atrium of the turtle heart, a study has been made of the effect of premature stimuli upon the rhythm of the heart.

If a stimulus is applied to the normal pacemaker in the sinus at such a time as to give rise to an immediate response, the next spontaneous response, as recorded from a point on the sinus close to the pacemaker, occurs at one normal beat interval after this. Subsequent responses follow at normal intervals thereafter.

If a stimulating electrode be placed so as to stimulate either atrium or sinus or both, according to the responsiveness of the tissue concerned at the moment of stimulation, and if lead-off electrodes be placed on the atrium, and if results be considered in terms of the time of the atrial response, it is found that a slightly premature stimulus results in a slight prematurity of atrial response, a slight lengthening of the succeeding cycle because of the compensatory pause, but no displacement of the pacemaker rhythm.

With further prematurity of stimulation, the pacemaker and atrium are stimulated simultaneously. The succeeding interval (as measured from the atrial record) is long but does not show further significant increase as the stimulus is placed earlier.

When the moment of stimulation is brought still earlier in the atrial cycle, the shock finds the atrium refractory but stimulates the pacemaker and causes a corresponding displacement of the rhythm. However, that premature sinus response may be conducted to the atrium, thus causing a premature response of the atrium. Since conduction of this impulse in the relatively refractory phases of sinus and atrium occupies a longer time than normal and since the conduction of the normal sinus beat to the atrium occurs in a normal time, both the cycles preceding and following the premature response will be measured as shorter than a normal cycle.

If stimulating electrodes are placed to touch the atrium but not the sinus, an early premature atrial beat may be elicited without causing a dropping of the next normal atrial beat which appears in its proper time.

AUTHOR.

Robertson, George H.: *Heart Disease in General Practice in New Zealand.* New Zealand M. J., June, 1936.

This is a survey of 700 consecutive patients suffering with heart disease who were seen in the course of general practice.

Complicating factors have been ignored, and in each case the original etiological factor only has been given so that each patient appears only once.

Criteria accepted for diagnosis have been those recommended by the Heart Committee of the New York Tuberculosis and Health Association.

An analysis of the case notes studied shows arteriosclerosis (32.0 per cent), hypertension (14.3 per cent), cardiac neurosis (21.1 per cent), thyrotoxicosis (11.6 per cent), and rheumatic fever (13.9 per cent) to represent over 90 per cent of the etiological factors.

AUTHOR.

Gladstone, Sidney A.: *Oxygen Utilization, Cardiac Output, and Related Circulatory Functions in Graves' Disease.* *Proc. Soc. Exper. Biol. & Med.* 34: 587, 1936.

In four cases of Graves' disease with an average basal metabolic rate of 33 per cent, the arteriovenous oxygen difference was found to be decreased by 37 per cent. The average cardiac output was 8.1 liters per minute compared with a normal of 4.2, representing an increase of 93 per cent. The relations of the present findings to those previously reported, to the question of method of cardiac output determination, and to the possible nature of the underlying metabolic disturbance in Graves' disease are briefly discussed.

AUTHOR.

Henderson, W. R., and Wilson, W. C.: *Intraventricular Injection of Acetylcholine and Eserine in Man.* *Quart. J. Exper. Physiol.* 26: 83, 1936.

A study is made of the direct injection of acetylcholine and eserine into the ventricles of human beings. The drugs, when injected in this manner, cause typical and similar reactions which are not reproduced by injection of the same amount of the drugs intravenously. The specific action of the drug is prevented or abolished by atropine. The authors conclude from these experiments that the responses of acetylcholine and eserine when injected intraventricularly are the result of action on the cerebral centers and not from peripheral action after absorption into the blood stream. The action of the eserine is thought to be due to inhibition of esterase, thus permitting the accumulation of acetylcholine which is being released at some of the synapses in the brain. Sleep was not produced in these experiments on human beings as was the case in previous work reported by Dikshit performed on cats.

E. A. H.

Altschule, Mark D., and Volk, Marie C.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Failure and Angina Pectoris: XVIII. The Cardiac Output Following Total Thyroidectomy in Patients With and Without Congestive Heart Failure, With a Comparison of Results Obtained With the Acetylene and Ethyl Iodide Methods. *Arch. Int. Med.* 58: 32, 1936.

Data on the changes in the cardiac output and related aspects of the circulation after total thyroidectomy in twenty-three patients are presented.

The output in volume per minute and the work of the heart are greatly diminished in hypothyroidism following total ablation of the normal thyroid gland.

The cardiac output decreases progressively to a greater extent than the oxygen consumption, as the basal metabolic rate falls in hypothyroidism. This disproportionate decrease in cardiac output is accompanied by a progressive increase in the arterio-venous difference. These changes are most striking when the basal metabolic rate has fallen below -15 to -20 per cent.

In nineteen of twenty-three patients the velocity of blood flow was slowed when the cardiac output was low. In patients with congestive failure the velocity of blood flow was much slower than in those without congestive failure. In three instances the velocity of blood flow did not reflect accurately the work of the heart.

The venous pressure, arterial pressure, and vital capacity were not significantly altered after total thyroidectomy in the patients in this series.

The measurements obtained for the same patients by the acetylene and ethyl iodide methods are compared. The results are the same by the two methods under the conditions of the experiments described.

Reduction in the work of the heart was associated with clinical improvement in the patients studied.

The data obtained in this study are in harmony with the concept that the relief obtained after operation in patients with angina pectoris is due principally to reduction of the work of the heart to, or below, an amount which it can do without the development of anoxemia.

In patients with congestive failure the basal oxygen consumption after total thyroidectomy falls well below the point at which it merely balances the low cardiac output, and the cardiac output at rest coincidentally becomes reduced below the pre-operative level. This makes it possible for the cardiac output in such patients to increase appreciably in response to work, so that the degree of activity may be increased without discomfort.

In addition, the marked diminution in basal cardiac work which occurs in all patients after operation affords the heart a significant measure of rest.

AUTHOR.

Jackson, D. E., and Jackson, Helen L.: Experimental and Clinical Observations Regarding Angina Pectoris and Some Related Symptoms. *J. Lab. & Clin. Med.* 21: 993, 1936.

Results of this study show that electrical stimulation inside the esophagus at appropriate locations within the chest produces muscular contractions and pain in exactly those areas of the body in which pain is developed during acute attacks of angina pectoris and coronary thrombosis. The innervation, the authors believe, is ipsilateral and does not come from the heart.

The authors believe that the ordinary explanation of angina pectoris being due to coronary artery spasm is erroneous. They believe that angina pectoris is due to acute incoordinated spasmodic contractions of the esophagus (including its longitudinal muscle layers) and stomach whereby gas or other stomach contents are



entrapped under pressure and the walls of either viscus, with their contained or adjacent nerves and tissues, are strained or injured. In this article they present a part of their experimental and clinical evidence to support these views and refer briefly to the relationship to coronary thrombosis.

AUTHOR.

Gross, Kurt: An Electrocardiograph for Quantitative Work for the Practitioner. *Ztschr. f. Kreislaufforsch.* 28: 269, 1936.

Description is given of a new portable electrocardiograph which does not distort the deflection, with a criticism of some other German models which do cause distortion.

L. N. K.

Wagenfeld, E.: Auricular Flutter Converted to Nodal Rhythm by Digitalis. *Ztschr. f. Kreislaufforsch.* 28: 433, 1936.

An unusual case is presented in which auricular flutter is converted during digitalization into auricular fibrillation and later into nodal rhythm with bigeminal beats. At times sinus arrhythmia occurred in this patient accompanied by S-A block.

L. N. K.

Katz, L. N., Gutman, I., and Ocko, F. H.: Alterations in the Electrical Field Produced by Changes in the Contacts of the Heart With the Body. *Am. J. Physiol.* 116: 302, 1936.

Experiments are reported in which various regions of the heart were connected to various parts of the chest by a good electrical nonpolarizable shunt. The alterations obtained were of two sorts (or intermediate or mixed forms): (a) diphasic additions when the region under the shunt electrode was not injured and (b) monophasic additions when the region under the shunt electrode was injured.

It is demonstrated that regions of the heart may gain a decided advantage over the rest of the heart merely because they are in contact with a good electrical conductor, provided that the contact is electrically nearer to one than the other of the two recording electrodes.

It is demonstrated that the point on the chest to which the heart currents are shunted determines the advantage of the heart region so shunted over the rest of the heart. This depends on the "electrical distances" between the recording electrodes and the point of shunt on the chest.

It is demonstrated that the electrical resistance of the shunting circuit determines the degree of advantage gained by the heart region shunted; the less the electrical resistance of the shunt, the greater the advantage.

It is suggested that the shunted region of the heart sets up its own electrical field in the body which summates with that set up by the heart through its natural contacts.

These experiments support the concept that the nature of the electrical conductors in contact with the heart are an important, if not the most important, element in determining the nature of the electrical field set up by the heart and thereby in determining the contour of the electrocardiogram obtained with recording electrodes at a distance from the heart. They also support the concept that alterations in the relation of various regions of the heart to the good electrical conductors and alterations in the location of the latter are important factors in modifying the ordinary electrocardiogram.

AUTHOR.

Katz, L. N., Sigman, E., Gutman, I., and Ocko, F. H.: The Effect of Good Electrical Conductors Introduced Near the Heart on the Electrocardiogram. *Am. J. Physiol.* 116: 343, 1936.

The introduction of good electrical conductors adjacent to the heart causes alterations in the electrical records obtained from direct, from distant, or a combination of direct and distant electrodes.

Evidence is given to suggest that the conductors introduced operate by (a) offering a by-pass for the currents generated by the heart, thereby decreasing the amount of current passing through the galvanometer circuit; (b) altering the path taken by the currents from the heart to distant points; (c) altering the relative contribution of the various regions of the heart to the recorded electrical curves; and (d) creating electrical stresses, the result of frictional electricity between dissimilar conductors.

The relative importance of these actions depends on (a) the manner of recording the electrical curves, (b) the presence or absence of regions of injury in the heart, and (c) the nature and location of the electrical conductor introduced.

These observations reemphasize and define, in part at least, the importance of the electrical properties of tissues adjacent to the heart in determining the electrical field set up by it.

AUTHOR.

Faxen, Nils: Paroxysmal Tachycardia and Bundle-Branch Block in a Boy of 11. *Acta paediat.* 18: 491. 1936.

The case described illustrates the value of electrocardiographic examination and at the same time shows an unusual complication with paroxysmal tachycardia in childhood. There was a history of rheumatism which probably accounted for the bundle-branch block. The etiology of the tachycardia is not explained. It is suggested that it may be a congenital defect.

H. McC.

Schwartz, Sidney P.: Studies on Transient Ventricular Fibrillation. III. The Prefibrillatory Mechanism During Established Auriculo-Ventricular Dissociation. *Am. J. M. Sc.* 192: 153, 1936.

The clinical and electrocardiographic manifestations in six patients with A-V dissociation who exhibited recurrent syncopal attacks due to transient ventricular fibrillation have been correlated.

In each instance it was determined that the alterations in the rhythm of the heart preceding a period of ventricular fibrillation were characterized by an acceleration of the basic ventricular rate of the ventricles.

The acceleration of the ventricular rate preceding ventricular fibrillation in patients with A-V dissociation was effected through: (a) a simple and progressive shortening of the interventricular periods; (b) a steplike progression of both auricles and ventricles with abrupt changes from partial to complete heart-block and vice versa, each alteration resulting in a further acceleration of the ventricular rate; (c) the interposition of a single extrasystole changing a slower rhythm to a faster one with a concomitant change in the pacemaker of the ventricles; (d) recurrent short runs of tachycardia arising in an ectopic focus of the ventricles and alternating with the periods of heart-block; (e) a tachysystole in which a rapid auricular rate kept pace with a rapid ventricular rate before fibrillation disrupted the whole cardiac mechanism; and finally (f) isolated premature beats of the ventricles which appeared in rapid succession and accelerated the heart before the cardiac mechanism responsible for syncope had set in.

On the basis of these correlated observations, it is fair to assume that a diagnosis of transient ventricular fibrillation may be suspected in a patient with A-V dissociation and syncopal attacks if any of these cardiac mechanisms are observed to appear either prior to or subsequent to syncopal seizures.

AUTHOR.

Webster, Bruce, and Cooke, Crispin: Morphologic Changes in the Heart in Experimental Myxedema. *Arch. Int. Med.* 58: 269, 1936.

Myxedema was readily produced in adult rabbits by total removal of the thyroid gland. In the cases of more severe involvement this was accompanied by pericardial and peritoneal effusions. The heart muscle of these myxedematous animals had an average fluid content of 81.9 per cent, as compared with 75.6 per cent in a control series of normal animals. On microscopic examination this heart muscle showed marked degenerative changes, characterized by a decrease in the number of fibers, edema, and a disappearance of the perinuclear sarcoplasm.

Myxedema is apparently capable of producing serious myocardial damage in the adult rabbit.

AUTHOR.

Hochrein, M., and Schneyer, K.: Prognosis of Myocardial Infarction. *Ztschr. f. Kreislaufforsch.* 28: 257, 1936.

Myocardial infarction is a serious concern of the cardiologist because of its high mortality and the restriction of activity in those who survive. The authors found a mortality rate of 71 per cent in their group of 226 cases. In 97 cases death occurred within a few days. During convalescence, 24 died of heart failure, 16 from the infarction, 7 from emboli, and 7 from secondary heart causes. There were 65 who survived, but only 23 without incapacity, while 22 had dyspnea on effort, 17 had stenocardia, and 14 had edema.

Of bad prognostic omen are (a) atypical clinical and electrocardiographic findings, (b) signs of secretory insufficiency, and (c) appearance of cardiac insufficiency. Normal vital capacity and a rapid return of blood pressure are favorable signs. Recovery is retarded by irregular habits, sexual excesses, and emotional upsets.

L. N. K.

Shookhoff, Charles, Douglas, Albert H., and Rabinowitz, Meyer: Sedimentation Time in Acute Cardiac Infarction. *Ann. Int. Med.* 9: 1101, 1936.

The red blood cell sedimentation time was studied in twenty-nine cases of acute cardiac infarction. It was abnormally rapid in all.

It became rapid between the second and fifth days and returned to normal between the thirteenth and thirty-ninth days.

An abnormal sedimentation rate may outlast the return of temperature and leucocyte count to normal by as much as four weeks. It may be abnormal when the temperature and leucocyte count have been normal throughout.

It is of great help in cases seen first several days or weeks after the occurrence of a cardiac infarction. It helps in the recognition of subsequent thrombosis or infection. It makes less arbitrary the duration of bed rest.

AUTHOR.

Mullins, William L.: Age Incidence and Mortality in Coronary Occlusion. *Pennsylvania M. J.* 39: 322, 1936.

The age incidence and mortality of 400 cases examined from the Heart Department of the Mercy Hospital, Pittsburgh, are tabulated. The immediate mortality in all cases was 9 per cent. In 80 cases seen between July, 1928, and July, 1930,

the immediate mortality was 7.2 per cent. Fifty-two of these patients are living at the present time. There was no immediate mortality in patients whose attacks occurred before age forty years. The immediate mortality increased gradually from ages forty to eighty years. Initial attacks occurred almost twice as frequently during the winter as during the summer months.

H. McC.

Schwarz, Hans G.: Concerning the Power of the Heart in Severe Congenital Involvement. *Ztschr. f. Kreislaufforsch.* 28: 385, 1936.

A case report is presented of an eleven-year-old child with severe congenital heart disease. Auricular fibrillation developed following pneumonia, but this lung infection led to no other evidence of damage to the heart.

L. N. K.

Summerfeldt, Pearl: Some Problems in Heart Disease in Childhood. *Canad. M. A. J.* 35: 165, 1936.

The author reviews the experiences of cardiac children at the Hospital for Sick Children in Toronto. The findings in this study are similar to those made in studies elsewhere. Emphasis is placed on the importance of respiratory and tonsil infection in relation to the etiology of rheumatic fever and heart disease.

H. McC.

Friedmann, R.: The Influence of Cardiac Valvular Disease Upon the Duration of Life. *Ztschr. f. klin. Med.* 130: 382, 1936.

The study is a numerical survey of the death rates of 1,164 patients with rheumatic valvular disease seen in the heart station in Vienna between June, 1919, and January, 1935. Analysis is made according to age, various types of valvular lesion, and size of heart. Comparison with the general death rate for Austria is given, and several interesting facts are set forth: most important among which are that (1) for all types of valvular disease together the death rate is slightly more than two and one-half times the general death rate, (2) combined mitral and aortic disease has the highest mortality rate ( $3\frac{1}{4}$  times the general death rate), and (3) aortic disease has the lowest mortality rate (less than twice the general death rate). The highest death rate for all types of valvular disease together occurred in the fifth decade ( $4\frac{3}{4}$  times the general death rate).

Many other more detailed comparisons are made. Two others deserve mention. The author cannot confirm the statements that the highest death rate is in the second and third decades following the rheumatic groups of infections; from his figures he decides that death rate depends rather upon the age of the patient. He also found that the duration of life becomes rapidly less with increase in size of the heart.

J. M. S.

Parhon, C. I., and Ornstein, J.: Preventive Treatment of Arteriosclerosis and Atheromatosis. *Schweiz. med. Wchnschr.* 65: 1164, 1935.

Arterial hypertension and hypercholesterolemia are two incontestable factors in the development of arteriosclerosis and atheromatosis. There is sufficient clinical and experimental basis for considering that certain endocrine dysfunctions are definitely associated with alterations in the blood cholesterol, namely, diseases of the ovaries, suprarenals, and thyroid gland. In exophthalmic goiter the mean level of the blood cholesterol is 161 mg. for each 100 c.c. of blood, in simple goiter it

is 200 mg., and in myxedema it is 190 mg. Other published articles show that in experimental and surgical thyroid deficiency there is an elevation of the blood cholesterol. It seems rational to consider that the treatment of hypercholesterolemia by the use of thyroid extract can be considered as preventive for the development of arteriosclerosis and atheromatosis. Five cases are reported in which the cholesterol of the blood was reduced by from 20 to 55 mg. after treatment with thyroxin orally, hypodermically, or intravenously. There was also a diminution in the total lipoids and fatty acids paralleling the decrease in the blood cholesterol and reduction in the water content of the tissue following the administration of thyroid.

N. W. B.

**Eberhard, T. P.: Effect of Alcohol on Cholesterol-Induced Atherosclerosis in Rabbits. Arch. Path. 21: 616, 1936.**

Through observation of the effect of alcohol per se on the rabbit fed cholesterol, the author hoped to shed some light on the widely held impression that drunkards do not show so much arteriosclerosis for given age groups as do temperate persons.

The cholesterol of the blood rose more rapidly and to higher levels in those animals which ingested both substances than in those which received cholesterol alone. The deposition of cholesterol in the tissues of liver and aorta, however, occurred in inverse ratio to the blood figures.

L. H. H.

**Haythorn, S. R., Taylor, F. A., Crago, H. W., and Burrier, A. Z.: Comparative Chemical and Histological Examinations of Aortas for Calcium Content. Am. J. Path. 12: 283, 1936.**

As a result of careful chemical determinations of metallic calcium and microchemical studies for visible calcium on fifty-two aortas from patients of varying ages, the authors found a consistent increase of calcium in aortas of patients beyond middle age in excess of that of other body tissues.

Von Kossa's silver method was found the most satisfactory microscopic indicator of the comparative amounts of calcium in sclerotic lesions.

The heaviest calcium deposits were in the abdominal portion. Positive microscopic tests began at the age of forty years and were 100 per cent positive in the specimens from patients between sixty-one and seventy years of age.

Mild intimal lesions may occur without any increase in calcium by chemical analysis.

L. H. H.

**Hallock, Phillip: Arteriosclerosis in Young Diabetics. A Method for Its Recognition by Arterial Elasticity Measurements. Am. J. M. Sc. 192: 371, 1936.**

The pulse-wave velocity method was utilized in studying arterial elasticity in the large and medium sized arteries of twenty-two young diabetics. To test the significance of the pulse-wave velocities obtained in this study the well-known Chi-square test was employed. While the values for the transmission of the aortic pulse wave did not indicate any significant changes from the normal, those for the transmission of the radial pulse wave were definitely significant.

The diabetic state either initiates early, or accelerates the development of premature, arteriosclerosis in the young adult.

AUTHOR.

Duff, G. Lyman: The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit. *Arch. Path.* 22: 161, 1936.

When arteriosclerosis was produced in rabbits after the method of Anitschkow, the first appearance of deposits of anisotropic lipoids occurred in spontaneous medial lesions of the aorta. Such spontaneous lesions remained free from such deposits in the control animals, to which no cholesterol fed rabbit deposits lipid first at the site of an arterial injury.

Photomicrographs and descriptions of the arteries are presented.

AUTHOR.

Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension. *Clin. Science.* 2: 209, 1936.

Under similar environmental conditions the rate of blood flow through the forearm is the same in subjects with essential hypertension, malignant hypertension, and chronic nephritis with hypertension as in subjects with normal blood pressures. The resistance offered by the vessels of the forearm is increased in these conditions owing to vasoconstriction, the blood viscosity being normal or less than normal. The increased vascular resistance is of such an order that, if generally distributed throughout the body, it would account for the levels of arterial pressure observed. After periods of circulatory arrest lasting up to ten minutes, the rate of blood flow through the forearm increases to the same extent in subjects with persistent hypertension as in normal subjects. It is concluded that in chronic nephritis and essential hypertension the abnormal agent narrowing the vessels is not nervous.

E. A.

Hutton, J. H.: Hypertension and Diabetes: Their Treatment by Radiotherapy. *Am. J. Roentgenol.* 55: 813, 1936.

For some years, the author has believed that essential hypertension and diabetes mellitus are due to some dysfunction, probably overactivity, of the pituitary or adrenal glands. He discusses the rationale of this contention and indications for treatment with radiotherapy. For two and a half years, a group of such patients has been treated, using varying dosages and numbers of treatments. Both sides of the pituitary and adrenals were treated at the same time. In many of the patients, there was a marked fall in blood pressure and almost complete symptomatic relief after the first treatment. In others the favorable results were slow, and in a few there was little or no effect from the treatment. There is frequently no correlation between the relief of the patient's symptoms and the reduction in the blood pressure. In certain of the patients there were interesting and favorable by-effects, such as correction of menstrual irregularities and relief of vasomotor phenomena in women who were treated during the menopausal state. Whether these effects are permanent, is not as yet determined.

E. A. H.

Bradshaw, H. H.: Fall in Blood Pressure During Spinal Anesthesia. *Ann. Surg.* 104: 41, 1936.

Experiments performed with the use of a colored solution of 10 per cent procaine crystals on five healthy and four completely sympathectomized cats indicate that the fall in blood pressure resulting from the subdural injection of procaine is due to paralysis of the vasoconstrictor nerve fibers. In the unsympathectomized animals, there was a marked fall in blood pressure following the subdural procaine injection but very little fall in the blood pressure of the sympathectomized

animals. From observations of the fall in blood pressure at different levels, it would appear that the vasoconstrictor fibers from the fifth thoracic level down are the most important factors in the type of blood pressure reaction occurring under spinal anesthesia. Measures indicated to prevent this blood pressure fall in humans are discussed.

E. A. H.

Motley, Lyle: Periarteritis. J. A. M. A. 106: 898, 1936.

The important features of this case are generalized involvement of somewhat migratory character, marked eosinophilia of peripheral blood, diagnosis during life and apparent recovery.

AUTHOR.

Dunphy, J. E.: Abdominal Pain of Vascular Origin. Am. J. M. Sc. 192: 109, 1936.

Evidence is presented to show that vascular disease of the mesentery can cause abdominal pain in the absence of gangrene or peritoneal irritation. It is suggested that pain so caused is the result of an anoxemia of the intestinal musculature and is a true visceral pain conducted by sensory neurones in the sympathetic nerves independently of the musculocutaneous pathways. The importance of recognizing the characteristics of this type of pain in the early diagnosis of mesenteric vascular occlusion (arterial) is emphasized.

AUTHOR.

Collins, Dean A.: Hypertension From Constriction of the Arteries of Denervated Kidneys. Am. J. Physiol. 116: 616, 1936.

Experiments in which the arterial blood pressure of male dogs is followed after constriction of both renal arteries and denervation of both kidneys indicate that the arterial hypertension thus produced is independent of the nervous connections of the kidney. The technic employed in constriction of the renal arteries is after the method of Dr. F. C. Mann. Completeness of the denervation is checked by histological examination for the presence of nerves in the structure of the renal pedicle. Renal function as tested by the nonprotein nitrogen and phenolsulphonephthalein renal function test is not significantly altered by bilateral renal artery constriction, nor are there any histological changes observable in the kidney.

E. A. H.

Cohen, Sidney Slater, and Barron, Maurice E.: Thrombo-Angiitis Obliterans With Special Reference to Its Abdominal Manifestations. New England J. Med. 214: 1275, 1936.

To the thirty-five published reports of autopsies on patients with thromboangiitis obliterans, the authors add four of their own. Necropsy evidence of thromboangiitis obliterans involving the vessels other than those of the extremities was found in several instances, which are grouped as follows: abdominal, 4 cases; coronary, 2 cases; hypogastric, 1 case; pulmonary, 1 case; intracranial, 1 case. Additional summary is given of eleven published cases of presumptive thromboangiitis obliterans of abdominal vessels; necropsies were not performed. One such case is added by the authors. It is important to keep in mind the possibility of involvement of the abdominal vessels when acute abdominal crises occur in patients with thromboangiitis obliterans.

H. M.

Marx, H.: Diseases of the Arterial System; Newer Experimental Results. *Deutsche med. Wchnschr.* 1: 502, 1935.

It is possible through stimulation of the hypophysial system to produce disturbances in renal function and an increase in blood pressure. In the blood, and particularly in the urine, of individuals with kidney disease, substances can be demonstrated which produce hematuria and hypertension and inhibition of diuresis similar to that produced by the posterior lobe hormone. Disturbance in the central regulation is not the only factor in the pathogenesis of kidney and blood vessel disease but other factors, such as infection, central nervous disturbances, and hormones, are important. There is a coordination of the various factors. All of them must be sought for and determined. The treatment of patients then is dependent upon all of these.

E. A.

Dittrich, R. J.: Peripheral Vascular Disease With Gangrene of Extremities. *Am. J. Surg.* 32: 533, 1936.

A vasospasm in a child of four years leading to serious trophic changes in hands and feet was relieved by surgical removal of masses of fat and fibrous tissue encroaching on the cervical and lumbosacral cord.

L. H. H.

Pyro, Reinhold: Significance of Various Types of Massive Limb Injury in Producing Gangrene. *Ztschr. f. Kreislaufforsch.* 28: 305, 1936.

The case reports include instances of frost-bite followed after an interval by gangrene caused by endarteritis obliterans and thrombosis, one case of Raynaud's disease with gangrene, one of erythromelalgia and one of cutis marmorata. A polemical discussion of the mechanisms involved is presented.

L. N. K.

Murray, D. W. Gordon: Embolism in Peripheral Arteries. *Canad. M. A. J.* 35: 61, 1936.

The author reviews the records of the Toronto General Hospital for the past five years, showing 126 cases of arterial embolism. He analyzes the series statistically and describes the important symptoms for diagnosis of such cases. Of these, he discusses fully pain, the color, temperature, sensory changes, paralysis, and pulsations in the affected part. He believes the diagnosis can usually be made without difficulty by careful observation of the clinical signs and symptoms.

In early cases embolectomy offers good results while neglected cases usually terminate with amputation or death.

H. McC.

Lummis, F. R.: Periarteritis Nodosa. *Ann. Int. Med.* 10: 105, 1936.

A case of periarteritis nodosa diagnosed during life and confirmed by biopsy is reported. The striking features were a long period of ill health with persistent fever, peripheral neuritis, muscular atrophy, renal impairment, gastrointestinal symptoms, and marasmus. Arsenic therapy reduced the temperature to normal but did not relieve the symptoms or arrest the progress of the disease.

E. A. H.



**Lewis, T.:** Pain as an Early Symptom of Arterial Embolism and Its Causation. Clin. Sc. 2: 237, 1936.

The early and often severe pain of embolism, or arterial thrombosis, is considered to be the result of ischemia of muscles in the limb. This conclusion has been based upon the facts that the pain is usually felt in the limb distal to the obstruction and because in nonmuscular organs, as the brain, lungs, and spleen, embolism or thrombosis is usually painless. The author obtained this information from a review of the literature and by direct observation on a number of his patients.

E. A. H.

**Edwards, H. T.:** Lactic Acid in Rest and Work at High Altitude. Am. J. Physiol. 116: 367, 1936.

Resting lactic acid values determined on blood drawn in the morning before rising show an initial slight rise over sea level values on going to high altitudes. Sea level values are found after acclimatization even at 6.14 km., where arterial saturations range between 55 and 70 per cent. .

Standard work performances, on first going to high altitudes, produce greater rises in blood lactic acid than at sea level. After acclimatization lactic acid values similar to those at sea level are found for a given performance. The ability to perform work is lessened progressively with increase in altitude, hence also the ability to accumulate lactic acid. Only slight increases over rest values of lactic acid are found during work at 6.14 km.

The inability to accumulate large amounts of lactic acid at high altitudes suggests a protective mechanism preventing an already low arterial saturation from becoming markedly lower by shift of the oxygen dissociation curve through acid effect. It may be that the protective mechanism lies in an inadequate oxygen supply to essential muscles, e.g., the diaphragm or the heart.

AUTHOR.

**Wilson, H. C.:** The Relation Between Rhythmic Variations in Blood Pressure and Rhythmic Contractions of the Artery of the Ear of Rabbits and Dogs. Am. J. Physiol. 116: 295, 1936.

The spontaneous rhythmic contractions in the main artery in the rabbit's ear have been studied in the preformed transparent chamber by Clark and Clark, and Wilson and others. In a new series of experiments simultaneous records of the blood pressure and observation of contractions of the main artery of the ear in rabbits and dogs have been made. In all of the experiments in this study whenever there were definite waves in the blood pressure, there were synchronous rhythmic contractions in the main artery of the animal's ear. It is impossible that the changes in the ear artery alone could account for the magnitude of the changes in the general blood pressure. Probably rhythmic changes in the blood vessels in various parts of the body are the cause of the blood pressure waves previously described. This would rule out a local origin for this phenomenon but not the possibility of some chemical agent being responsible for these rhythmic changes. The inhibitory effect of anesthetics and the stimulating effect of morphine on these rhythmic contractions are described.

E. A. H.

**Mahorner, H. A., and Ochsner, A.:** A New Test for Evaluating Circulation in the Venous System of the Lower Extremity Affected by Varicosities. Arch. Surg. 33: 479, 1936.

The current tests used for evaluation of circulation in varicose veins are discussed. A new test is described for determining the direction of flow of blood in

the venous system in the lower extremities affected by varicosities and for determining the competency of the valves of the long saphenous vein and the connecting veins between the superficial and deep systems of the thigh. The test is of value in determining the most suitable type of therapy and the possibilities of recurrence after treatment.

E. A. H.

Saylor, Leslie L., and Wright, Irving S.: Studies on Two Cases of Urticaria From Cold Sensitivity and of the Effect of Histamine Treatment. *Am. J. M. Sc.* 192: 388, 1936.

Two cases of urticaria, both in females, from cold sensitivity are reported.

In the first case rather extensive experimental studies were possible. The beneficial effects of histamine treatment were observed.

That the reaction occurred at an unusually high skin temperature in this case was demonstrated.

Experiment points toward the humoral hypothesis of cause of reaction.

The second case is reported primarily because of the complete collapse when the patient was swimming in cold water.

AUTHOR.

Robertson, Harold F., and Fetter, Ferdinand: The Effect of Venesection on Arterial, Spinal Fluid, and Venous Pressures With Especial Reference to Failure of the Left and Right Heart. *J. Clin. Investigation* 14: 305, 1935.

A series of experiments was carried out to determine the relation of arterial, spinal fluid, and venous pressures before and after venesection.

It was found in right heart failure that venous and spinal fluid pressures were elevated and related with respect to fall of pressures induced by venesection. The variation in the ratio between the two pressures is shown by the divergences from a linear distribution.

The spinal fluid pressure was elevated above normal in 32 per cent and 85 per cent of left and right heart failures, respectively. No correlation obtained between the arterial blood pressure and the venous or spinal fluid pressures in either right or left cardiac incompetence. The venous and spinal fluid pressures were uncorrelated in failure of the left heart. The spinal pressure was greater than the venous pressure in all of 140 observations made on 35 patients.

AUTHOR.

Greene, Charles W.: The Nervous Control of the Coronary Circulation and Its Clinical Significance. *South. M. J.* 29: 478, 1936.

The coronary blood vessels are richly supplied with efferent neurons of both coronary dilator and coronary constrictor type. Of these, the coronary dilator neurons are greater in mass effect, more definite in physiological control, and must obviously serve the primary function of increasing the coronary flow during augmented myocardial work.

Coronary constrictor mechanisms, on the other hand, are more limited, the reaction is less voluminous; but in extreme development this portion of the cardiac mechanism may play an important part in producing attacks of functional angina.

The new concept, that these two great coronary nerve mechanisms are delicately controlled by very definite and specific reflex nervous mechanisms in adaptation to every delicate changing activity of the whole body. These reflexes are primarily coronary dilator in type; nevertheless there may occur associated reflex coronary constrictions.

In pathology of the myocardium, and especially of the coronary vessels, structural changes inevitably reduce physiological resilience and delicacy of adaptive response. Under conditions in which the normal animal reacts by increases in the coronary circulation corresponding to the increase in myocardial work, the pathological heart cannot give the corresponding dilatations of the coronary arterial system. Hence there is failure of adequate coronary blood flow, and cardiac asphyxiation follows. Oxygen want is induced with the resulting spasms of pain.

Of the two processes which can induce anginal attacks, the overfunctional activity of the reflex coronary constrictor mechanisms seems to be of lesser significance than the blocking of functional dilatations by pathology of the vessel walls.

AUTHOR.

Albrecht, H. U.: Concerning the X-ray Diagnosis of Aneurysms of the Sinus Valsalvae of the Aorta. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 53: 218, 1936.

This report is based on three cases, one of which is proved by autopsy. The author discusses the radiological signs of aneurysm of the sinus valsalvae. They occur more commonly in the right sinus valsalvae and develop on the right side or anteriorly. They are found roentgenologically as saclike shadows protruding into the right lung field or into the anterior mediastinum, where they may produce erosions of the the aortic valve was made during life.

AUTHOR.

Delherm, L., and Fischgold, H.: Four Years of Cardiovascular Radiokymography. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 53: 223, 1936.

The main diagnostic advantages of the kymographic method are its ability to differentiate between aortic aneurysm and mediastinal diseases, to detect diseases of the pulmonary artery, and to differentiate between the vena cava and the organs which contribute to the formation of the cardiovascular silhouette. The method allows one to judge the tonicity and the contractile power of the left ventricle and to analyze the occurrences of extrasystoles, pulsus alternans, and bigeminus.

F. B.

Dahm, M., and Meese, J.: Concerning the Movement of the Mediastinum in Aortic Aneurysm. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 53: 265, 1936.

This is a report of observations of aneurysms of the arcus aorta with stenosis of the left main bronchus with demonstration of the movement of the mediastinum observed in the kymogram. A difference exists in the kymographic appearance of the mediastinal movement in lung tumors and in aortic aneurysms.

F. B.

Blackford, L. Minor, Bryan, William W., and Hollar, Emory D.: Calcification of the Aortic Valve. *J. A. M. A.* 107: 18, 1936.

In a negro, aged thirty-seven years, with a long history of cardiac pain and a relatively short history of congestive heart failure, the diagnosis of calcification of sternum.

F. B.

Leriche, Rene, and Fontaine, Rene: Indications, Results and Technic in Arteriectomy. *Presse méd.* 97: 1953, 1935.

Arteriectomy was performed in 80 cases by the authors during ten years. When an artery becomes thrombosed, its function not only ceases, but it may also act as a focus for peripheral vasoconstriction. Arteriectomy is followed by definite

and lasting vasodilatation as shown by changes in skin temperature and by arteriography. Experiments on dogs show that localized obstruction of an artery produces much more impairment of circulation than resection does. Thrombosis in large arteries is likely to produce not only peripheral vasoconstriction but also secondary peripheral arterial thrombosis at a distance and without continuity with the original thrombosis. Resection of the obliterated arterial segment prevents the vasospasms and produces definite vasodilatation.

In carrying out the resection of the thrombosed artery, it is necessary that the entire thrombosed segment be removed. Therefore, if the thrombosis is very extensive, resection may be impossible. At the onset of thrombosis, the obliteration may be quite limited, and surgical intervention should be carried out early before thrombosis has extended. Localization of the lesion is possible only by arteriography. Arteriectomy should be done only if the obliteration in the artery is complete. It is necessary that the arterial resection be carried out without injuring the origin of the neighboring collateral arteries above and below the lesion. Arteriectomy was carried out in four cases of traumatic obliterations of arteries. Surgical intervention should not be delayed in such cases. Arteriectomy is valuable in treatment of Volkmann's syndrome and of thromboses secondary to cervical rib. If embolectomy is not possible due to delay in seeing the patient, arteriectomy may be the method of choice in the treatment of embolic occlusion. However, in cases in which much time has elapsed and there are signs of impending gangrene, the operation is not successful. In syphilitic arteritis the operation was performed twice, but the subjects died of coronary occlusion. In thromboangiitis obliterans, 34 arteriectomies were done, with 10 failures; 7 had transient improvement of at least three months' duration; 2 had good results, but were not restored to work; and 6 had very good results with disappearance of symptoms and were able to resume their occupations. In arteriosclerosis obliterans, the results were even better, although one patient of the 34 operated on died of gas gangrene. Eight had excellent results, 10 good results, 8 transient benefit only, and 2 showed failures. Operations were often done in the advanced stage of obliterative arterial disease. The arteries upon which the operations were performed were as follows: superficial femoral, 60; external iliac, 3; popliteal, 5; brachial, 9; posterior tibial, 2; anterior cubital, 1. Arteriectomy of the posterior tibial and popliteal arteries may be attended with serious complications, particularly if the obliterative disease is extensive. The best results have attended the resection of the superficial femoral artery. Recognition of the localization of the lesions in this vessel can be made by arteriography, and the authors operate only after they have made arteriograms with thorium dioxide. This allows them to note the exact location of the obliteration, its extent, and the condition of the collateral circulation. If arteriography shows a very poor collateral circulation, arteriectomy is not performed.

The technic of the operation for arteriectomy of the superficial femoral artery is described.

N. W. B.

## Book Review

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CLINICAL HEART DISEASE. By Samuel A. Levine, M.D., F.A.C.P. Philadelphia and London, 1936, W. B. Saunders Company, 445 pages, 97 figures.

The author states that the purpose of the book is to present, in a simple form, the important aspects of the diagnosis, prognosis, and treatment of heart disease. It is meant to appeal to the general practitioner. No attempt was made to cover in detail the entire field of cardiovascular disease. None of the usual plans of arrangement were adopted. Each chapter is to be regarded as distinct in itself, a brief treatise on the subject. No bibliographic references are included.

The author writes interestingly. He has a simple, direct, literary style, knowledge of his subject, original ideas, and willingness to make dogmatic statements. These qualities make his book a pleasure to read. Most interesting of all are the author's views on matters not yet fully established. The fact that most views regarding disease, unsupported by proof, are sooner or later found to be wrong does not lessen one's interest in reading them.

The chapter on clinical electrocardiography is particularly good, and the reviewer is glad to state that he met with no success in detecting errors of interpretation. The chapters on rheumatic fever and the development of rheumatic heart disease, angina pectoris and coronary thrombosis will prove particularly useful for the general practitioner. On the other hand, a few adverse comments seem justified. It is to be regretted that there is no chapter on cardiac roentgenography. Cardiovascular syphilis, although it may not flourish in the austere atmosphere of Boston, would seem important enough, nevertheless, to warrant more than six pages of discussion in a book on heart disease. Nearly all articles on coronary arteriosclerosis and its complications are contributed by specialists who are likely to be consulted for attacks of stenocardia. This makes them throw angina pectoris and coronary thrombosis into the spotlight, whereas these processes are in reality merely intermediate or terminal episodes in the relentless march of coronary arteriosclerosis toward heart failure. This book is no exception to the rule. One does not obtain an adequate picture of this important disease.

The book may be read with profit not only by general practitioners who wish to acquaint themselves with the subject of cardiology, but also by internists, including cardiologists. As a matter of fact, one ventures to predict that the cardiologists, especially those who are a little weak on the clinical side, will derive as much benefit as anyone else.

C. C. W.

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## Erratum

In the article, "The Relationship of Tachycardia to Cardiac Insufficiency," by Drew Luten, M. D., in the October issue of the JOURNAL, the sentence beginning on line 14, page 441, should read, "It is known that as the *ventricle fails*, irritability increases," 16, 17, 18 and that with improvement it diminishes again."

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## Original Communications

### THE COMMONEST CAUSE OF HYPERTROPHY OF THE RIGHT VENTRICLE—LEFT VENTRICULAR STRAIN AND FAILURE\*

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BOSTON, MASS.

IN 1933 White and McGinn<sup>1</sup> emphasized the importance of the recognition of the clinical aspects of left ventricular strain and failure without failure of the right ventricle of the heart. They pointed out "the astonishing fact that so little attention has been paid by the English-speaking world . . . to this state of congestive failure of the left ventricle without congestive failure of the right ventricle." As a logical corollary to this conception, we have become interested in the effect that pure left ventricular strain, due to chronic arterial hypertension, aortic valvular disease, and infarcts of the left ventricle, may have in producing hypertrophy of the right ventricle which is not subjected to the primary strain.

It is known that general enlargement of the heart may occur in pure left-sided strain, for at autopsy there is often an appreciable enlargement of the right ventricle, as well as of the left, in patients whose hearts were presumably subjected only to left ventricular strain. The sequence of events which produces this right-sided enlargement has been clearly summarized by Wiggers,<sup>2</sup> who pointed out that, when the left ventricle begins to weaken and fail, it "dilates enormously," and that "this marks the onset of cardiac fatigue. Straub's experiments indicate that when this occurs the pressures in the left auricle become greatly elevated and the lungs markedly distended." It should be added that dilatation of the left ventricle may be associated with the production of a relative mitral valve regurgitation, merely through stretching of the mitral ring. Wiggers further states that

\*From the Cardiac Laboratory and Clinics of the Massachusetts General Hospital. Read in Abstract at the Annual Meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1936.

†Dalton Scholar, Massachusetts General Hospital, 1935-36.

"the right ventricle, in consequence, is compelled to contract against a greater load; it then passes through the same phases of cardiac strain as the left." We have, then, an adequate explanation for right ventricular enlargement when the left ventricle has been the primary seat of the strain. According to Wiggers, "the enlargement may affect the entire heart, but naturally occurs predominantly in the ventricle which is called upon to bear the brunt of the excess work." There is no doubt that this statement is true, but two cases\* have recently come to our attention in which the predominant hypertrophy was on the right side, while the left side had been the primary seat of the strain. We shall review them briefly.

The first case was a man, aged forty-three years, with aortic stenosis and insufficiency without other valvular disease, who had had marked congestive failure of both ventricles for eighteen months. The electrocardiogram revealed *right axis* deviation of marked degree. At post-mortem examination there was actually preponderant hypertrophy of the right ventricle, its wall measuring 8 mm. in thickness (normal 3), while the left measured 17 (normal 10). The heart was markedly enlarged, its weight being 910 gm. No factor producing primary right ventricular strain was found.

The second case was similar. The patient was a man, aged thirty-eight years, who had had severe congestive failure of both ventricles for three months. He also had aortic stenosis and insufficiency, and his electrocardiogram revealed a moderate degree of *right axis* deviation. Again the right ventricle was preponderantly hypertrophied, its wall measuring 11 mm., while the left measured 22 mm. The heart weighed 750 gm.

Obviously these two cases do not represent a usual occurrence in left ventricular strain, but they do demonstrate that the side of the heart which is free from the primary strain may be not only considerably hypertrophied, but that its hypertrophy may actually be preponderant.

The present study is concerned with the causes of hypertrophy of the right ventricle and the importance of pure left ventricular strain in producing this hypertrophy. Our procedure has been to study cases in which right ventricular hypertrophy had been demonstrated at post-mortem examination, and to determine, from both the clinical and the post-mortem data, the seat of the strain. We are concerned, then, with right ventricular hypertrophy per se, and not with preponderant hypertrophy, since, for the moment, the degree of left ventricular hypertrophy remains out of consideration.

The protocols of 2,524 consecutive autopsies at the Massachusetts General Hospital† were reviewed, and all cases in which the right

\*We are indebted to Dr. S. B. Wolbach, of the Department of Pathology at the Peter Bent Brigham Hospital, for permission to cite these cases.

†Our thanks are due to Dr. Tracy B. Mallory, chief of the Department of Pathology for allowing us to use his files and records.

ventricular wall measured 5 mm.\* or more in thickness were selected for study. Partial examinations which did not include the heart and examinations of infants and children were excluded (a total of 524 cases), so that 2,000 adult hearts remained for review. Among these 2,000 cases there were 704 with hypertrophy of the right ventricle. These 704 cases were then divided into four groups: first, those in which there had been primary right ventricular strain; second, those with primary left ventricular strain; third, those with primary strain on both sides of the heart; and fourth, those in which we could find no clear factor of strain on either side of the heart. The factors that we have considered responsible for these various kinds of strain are shown in Table I.

TABLE I  
FACTORS PRODUCING STRAIN ON THE HEART

PRIMARY LEFT VENTRICULAR STRAIN	PRIMARY RIGHT VENTRICULAR STRAIN	PRIMARY STRAIN ON BOTH VENTRICLES
Arterial hypertension	Mitral stenosis	Mitral insufficiency
Aortic stenosis	Pulmonic valve stenosis	Multiple valvular disease
Aortic insufficiency	Pulmonic valve insufficiency	(chiefly aortic and mitral)
Infarction of the left ventricle	Pulmonary endarteritis	Severe anemia
	Organic tricuspid insufficiency	Arterial hypertension, aortic valve disease, or myocardial infarction
	Marked pulmonary fibrosis	<i>plus</i> factors producing right ventricular strain
	Marked pulmonary emphysema	
PRIMARY STRAIN ON LEFT VENTRICLE AND SECONDARY STRAIN ON RIGHT VENTRICLE		
Factors listed in the first column above plus failure of the left ventricle		

Table II shows the number of cases in each of these groups, each group being divided according to the degree of right ventricular hypertrophy as shown by the thickness of the wall.

In about one-fourth of the cases, those in the last column, we could find no factor of strain which allowed us to place them in one of the other groups. Many of these hearts had coronary artery disease without occlusion or myocardial infarction, cases which perhaps might fairly have been classed as having left ventricular strain (since the coronary supply to the left ventricle is ordinarily more extensively involved in a sclerotic process than is that to the right), but without infarction of the left ventricle we have not felt ourselves justified in so grouping them. Without doubt, some of the patients whose hearts we have listed as having been under no strain did have arterial hypertension, their blood pressures being normal or low while they were in

\*This thickness was chosen on the basis that the normal right ventricle measures 3 and sometimes 4 mm. in thickness.

The thickness of the right ventricular wall is routinely measured at a point on the anterior surface midway between the apex and the base of the ventricle.



TABLE II

CLASSIFICATION OF CASES IN WHICH THE RIGHT VENTRICULAR WALL MEASURED 5 MM. OR MORE IN THICKNESS

RIGHT VENTRICULAR WALL	TOTAL NUMBER OF CASES	PURE RIGHT VENTRICULAR STRAIN	STRAIN ON BOTH VENTRICLES	PURE LEFT VENTRICULAR STRAIN	NO CLEAR STRAIN ON EITHER VENTRICLE
5 mm.	345	25	57	154	109
6 mm.	203	12	37	108	46
7 mm.	77	7	21	36	13
8 mm.	42	6	16	16	4
9 mm.	12	2	1	8	1
10 mm.	8	2	5	1	0
11 mm.	8	6	0	2	0
12 mm.	5	2	2	1	0
13 mm.	1	0	1	0	0
14 mm.	2	1	1	0	0
16 mm.	1	1	0	0	0
Total	704	64	141	326	173

the moribund state presented during their stay in the hospital. Again, unquestionably there are a number of normal hearts in this column, hearts with a normal weight from patients without clinical or pathological evidence of heart disease. This latter group leads us to believe that in a few instances the normal right ventricle may measure as much as 5 mm. in thickness.

For purposes of comparison we have combined the cases with pure right ventricular strain with those in which there was strain on both sides of the heart, so that all cases with any element of primary right-sided strain may be compared with those in which there was pure left-sided strain. This comparison is shown in Table III. In about 61 per cent of the cases with right ventricular hypertrophy, the cause

TABLE III

ALL CASES WITH STRAIN. CASES WITH PRIMARY RIGHT VENTRICULAR STRAIN AND THOSE WITH PRIMARY STRAIN ON BOTH VENTRICLES HAVE BEEN COMBINED FOR COMPARISON WITH THOSE HAVING PURE LEFT VENTRICULAR STRAIN

RIGHT VENTRICULAR WALL	TOTAL WITH RIGHT VENTRICULAR STRAIN	PURE LEFT VENTRICULAR STRAIN
5 mm.	82	154
6 mm.	49	108
7 mm.	28	36
8 mm.	22	16
9 mm.	3	8
10 mm.	7	1
11 mm.	6	2
12 mm.	4	1
13 mm.	1	0
14 mm.	2	0
16 mm.	1	0
Total	205	326

is seen to be strain on the left ventricle. This figure would very likely be even greater if we had considered coronary artery disease without myocardial infarction as a cause of left ventricular strain, and if the antecedent blood pressures in the moribund patients were known.

Inspection of Table III shows that when a high degree of hypertrophy of the right ventricle is found, there has probably been some factor producing primary right ventricular strain. In Table IV we have added together all cases in which the right ventricular wall measured 5 mm. or more, 6 mm. or more, and so on. It is apparent that even when the measurement is 6 mm. or more, left ventricular strain is still the more important cause. When measurements of 7 mm. or more are considered, there are approximately equal numbers of cases in both groups. It is only when marked hypertrophy with measurements of 8 or 9 mm. or more is considered that primary right ventricular strain becomes appreciably more frequent as the cause. It is notable, however, that measurements as great as 12 mm. for the right ventricle were found when the strain had been at first purely left-sided.

TABLE IV

IMPORTANCE OF PURE LEFT VENTRICULAR STRAIN IN PRODUCING THE VARIOUS DEGREES OF RIGHT VENTRICULAR HYPERTROPHY

ALL CASES WITH THE RIGHT WALL MEASURING	NUMBER OF CASES	
	RIGHT VENTRICULAR STRAIN	PURE LEFT VENTRICULAR STRAIN
5 mm. or more	205	326
6 mm. or more	123	172
7 mm. or more	74	64
8 mm. or more	46	28
9 mm. or more	24	12
10 mm. or more	21	4
11 mm. or more	14	3
12 mm. or more	8	1
13 mm. or more	4	0

*Effect of Failure of the Left Ventricle Upon the Degree of Right Ventricular Hypertrophy.*—Presumably, when the left ventricle is under the strain of arterial hypertension, aortic valvular disease, or myocardial infarction, this strain should not produce pulmonary engorgement and secondary right ventricular strain so long as the left ventricle is able to adjust itself to this strain. We should not, then, expect to find hypertrophy of the right ventricle under such circumstances. In order to study this point, we have reviewed all cases in the files of the Massachusetts General Hospital Department of Pathology which had been diagnosed hypertensive heart disease, aortic valvular disease, and old infarction of the left ventricle. These cases were selected without regard to the presence or absence of hypertrophy of the right ventricle. The clinical records were then examined for symp-

toms and signs of heart failure. Dyspnea, even without other symptoms or signs, was considered evidence of left ventricular failure, and was usually the first to appear. The cases were then divided into two groups: first, those which had never had failure, or had had it only as a terminal event, beginning in no instance more than two weeks before death; and second, those which had had symptoms or signs of left ventricular failure for two months or more. This period of two months was arbitrarily chosen because we felt that it should be sufficient to allow hypertrophy of the right ventricle in response to a newly imposed strain. A large intermediate group was discarded. Table V shows the average thickness of the right ventricular wall in these two groups.

TABLE V  
CASES WITH PURE LEFT VENTRICULAR STRAIN

	NUMBER OF CASES	AVERAGE THICKNESS OF RIGHT VENTRICULAR WALL
No clinical evidence of failure	44	4.8 mm.
Failure of left ventricle	91	5.5 mm.

Two things are evident from Table V: first, that in cases with pure left ventricular strain, the right ventricle hypertrophies regardless of the presence or absence of clinical evidence of failure of the left ventricle; and second, that the superimposition of failure adds to the degree of right ventricular hypertrophy. The explanation for this second fact is obvious and in accord with what was anticipated. Why right ventricular hypertrophy should occur in well-compensated left ventricular strain is not at first entirely clear. Very likely some of the cases we classed as showing no failure did have failure, and the facts were not accurately recorded in the case histories, but this should not be so in any appreciable number of them. More probably, there is frequently a state of slight pulmonary vascular engorgement, and consequent strain on the right ventricle, in cases with pure left-sided strain, even though dilatation of the left ventricle and mitral ring has not occurred and there is no functional mitral regurgitation. A slight increase in pulmonary arterial pressure, without more evidence than that of failure of the left ventricle, would then seem likely and is in keeping with the observed facts.

*Comparison of the Degree of Right Ventricular Hypertrophy in Pure Left Ventricular Strain With That in Right-Sided Strain.*—For this comparison, an additional group of cases having primary right ventricular strain was selected from the files, no attention being given to the presence or absence of right ventricular hypertrophy. These were similarly divided into two groups, those without symptoms or signs of pulmonary engorgement (such as might result from the obstruction caused by mitral stenosis), and those with such symptoms or

signs for two months or more. The averages are shown in Table VI. It is evident again that pulmonary engorgement increases the degree of hypertrophy seen in the right ventricle. It is worthy of note, however, that on the average, the right ventricle is hypertrophied almost as much in well-compensated left ventricular strain as it is when there has been primary right ventricular strain, as shown by the two average figures, 4.8 and 5.0 mm. It seems reasonable, therefore, to regard an average thickness of 4.8 mm. for the right ventricular wall as indicative of hypertrophy.

TABLE VI

	NUMBER OF CASES	AVERAGE THICKNESS OF RIGHT VENTRICULAR WALL
Without obvious failure or pulmonary engorgement		
Right ventricular strain	47	5.0 mm.
Pure left ventricular strain	44	4.8 mm.
With failure or pulmonary engorgement		
Right ventricular strain	51	6.0 mm.
Pure left ventricular strain	91	5.5 mm.

TABLE VII

PURE LEFT VENTRICULAR STRAIN:  
RELATIONSHIP BETWEEN THE THICKNESS OF THE RIGHT AND LEFT  
VENTRICULAR WALLS\*

THICKNESS OF RIGHT VENTRICULAR WALL	THICKNESS OF LEFT VENTRICULAR WALL IN MILLIMETERS																															
	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	30	32									
5 mm.	1	-	4	3	9	9	10	18	14	15	28	7	17	4	4	2	-	-	-	-	1	-	-									
6 mm.	1	3	-	1	1	2	5	11	12	9	16	8	12	3	6	4	5	3	-	2	-	2	1									
7 mm.	-	-	1	-	-	1	3	3	2	5	3	2	4	2	1	3	1	-	-	-	1	2	-									
8 mm.	-	-	-	-	-	-	-	-	1	3	1	-	6	-	1	1	-	-	-	-	-	-	-									
9 mm.	-	-	-	-	-	-	1	-	-	-	2	-	-	-	2	-	2	-	-	-	-	-	-									
10 mm.	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-									
11 mm.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-									
12 mm.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-									

\*Each figure indicates the number of cases with a given thickness of each of the ventricular walls; thus, there were 18 cases in which the right ventricular wall was 5 mm. and the left 15 mm. in thickness.

*Preponderant Hypertrophy of the Right Ventricle in Pure Left Ventricular Strain.*—Table VII shows that there were a number of cases in which the comparative measurements of the two ventricular walls suggest preponderant hypertrophy of the right ventricle when the strain had been wholly left-sided. There were, in fact, twenty cases in which the right ventricle was fully half as thick as the left ventricle. This is a striking relative increase in the thickness of the right

ventricle when one considers that the normal figures are in the neighborhood of 3 to 4 and 9 to 10 mm. for the right and left walls, respectively.

Among the ninety-four electrocardiograms without intraventricular or bundle-branch block that were available in the cases with pure left-sided strain, there were four with right axis deviation and many more that failed to show the left deviation that would be expected in such strain. In the four cases with right deviations, the measurements for the right and left ventricles were 8 and 16 mm., 6 and 19 mm., 6 and 15 mm., and 6 and 19 mm. In two of these four cases there was considerable dilatation of the right ventricle, while in two no mention was made of the size of the cavities. In these cases there was doubtless preponderant enlargement of the right ventricle, even though the measurements may not prove it. It is unfortunate that more electrocardiograms were not available, for had there been, additional instances of right axis deviation would probably have been found.

#### COMMENT

We are, of course, aware of the unreliability of the thickness of a ventricular wall as the sole guide to the degree of its hypertrophy. Herrmann and Wilson<sup>3</sup> in their dissections of fifty-nine hearts, showed great variations in the weights of the ventricles, when weighed separately, for a given thickness. It is obvious that a right ventricle measuring but 4 mm. in thickness may have a weight greatly above the normal if the cavity is markedly dilated, and that it may weigh even more than a wall measuring 6 or 7 mm. in thickness surrounding a cavity of normal size. We believe, however, that our conclusions, drawn from this large number of cases, are valid, since dilatation of the right side of the heart was so frequently found in the cases with increased thickness of the right ventricular wall.

Errors in the interpretation of the measurements may arise from failure to note the state of myocardial relaxation or contraction during post-mortem examination, although this should lead to little error when dealing with a large series, since it is uncommon to find a heart in systole at autopsy. In not more than three or four instances was such a state noted in our cases, while almost invariably the comment was made that the myocardium, particularly that of the right ventricle, was relaxed and flabby, dilatation often being marked.

We believe that it is particularly significant that this collection of cases comes from New England, where rheumatic heart involvement (usually mitral disease which causes right ventricular strain) is very common. White and Jones<sup>4</sup> found in 1928 that this etiology was responsible for 54 per cent of the heart disease in patients coming to the Massachusetts General Hospital with cardiovascular symptoms.

In other localities, left ventricular strain would be an even more frequent cause, relatively, of right ventricular hypertrophy.

This study adds weight to the recent work of Harrison<sup>5</sup> in emphasizing the "back pressure" theory of congestive heart failure. We believe also that it adds emphasis to left ventricular strain and weakness as a cause of more far-reaching effects than is commonly appreciated, and that strain, hypertrophy, and failure of the right ventricle are dependent more frequently upon the same processes in the left ventricle, which have preceded by some weeks or months, than they are upon other factors. We have, then, further corroboration of the importance of the recognition of the effects of left ventricular strain and of the conception of left ventricular failure, which have so long been neglected in English medical literature.

#### SUMMARY

Among 2,000 consecutive post-mortem examinations, 704 cases had hypertrophy of the right ventricle to the extent that the wall measured 5 mm. or more in thickness. In about one-fourth of these, no strain on either side of the heart was clearly evident. In 61 per cent of the remaining cases, the strain on the heart had been due to arterial hypertension, aortic valvular disease, or infarcts of the left ventricle, and no factor producing primary right ventricular strain could be found. Left ventricular strain was, then, the commonest cause of hypertrophy of the right ventricle.

Hypertrophy of the right ventricle was often found in cases with pure left-sided strain, regardless of the presence or absence of clear clinical evidence of failure of the left ventricle, but the presence of failure increased the degree of hypertrophy.

The degree of hypertrophy of the right ventricle was almost as great in cases with pure left-sided strain as it was when there had been primary right-sided strain.

A few examples of preponderant hypertrophy of the right ventricle were found in cases with pure left-sided strain in this series. Four of these had electrocardiograms showing right axis deviation. We have encountered two other similar cases, not in the series analyzed above.

#### REFERENCES

1. White, P. D., and McGinn, S.: The Importance of the Clinical Recognition of Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle, *Tr. A. Am. Physicians* 48: 104, 1933.
2. Wiggers, C. J.: *Circulation in Health and Disease*, ed. 2, Philadelphia, 1923, Lea & Febiger, pp. 562 and 570.
3. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy, Comparison of Electrocardiographic and Post-Mortem Observations, *Heart* 9: 91, 1921-2.
4. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *AM. HEART J.* 3: 302, 1928.
5. Harrison, T. R.: *Failure of the Circulation*, ed. 1, Baltimore, 1935, Williams and Wilkins Co.

# DISSECTING ANEURYSMS OF THE AORTA

WITH A REPORT OF FIVE CASES\*

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**D**ISSECTING aneurysms are supposed by most clinicians to be rare conditions, of interest only to pathologists. In 2,763 autopsies at the Roper Hospital from Jan. 1, 1914, to July 1, 1935, there have been five cases of dissecting aneurysm of the aorta, an incidence among those autopsied of 0.18 per cent. Shennan<sup>1</sup> reports 11 cases in a total of 1,922 post-mortem examinations at Aberdeen from January, 1918, to December, 1932, an incidence of 0.57 per cent. As a matter of fact, dissecting aneurysms are probably more common than even pathologists realize, as it is likely that not a few cases of sudden death, commonly ascribed to "a heart attack" and not autopsied, are of this nature.

Shennan, in his admirable survey of the subject in 1934, collected 297 cases of dissecting aneurysm of the aorta from the literature, including the famous case of George II. A few cases of dissection have been reported in the pulmonary artery and a few in peripheral vessels.

## FACTORS LEADING TO DISSECTION

Most of the reported cases that are available for study, and in which case records are satisfactory, give a previous history of hypertension, and cardiac enlargement is usually present.

Disease of the aortic walls is generally believed to be the most important factor predisposing to dissection. This is usually of the nature of an atherosclerosis. As is commonly known, atherosclerosis does its greatest damage to the intima and the inner layers of the media, leaving the outer portions of the media and the adventitia relatively uninvolved. On the other hand, syphilis usually does its greatest damage in the adventitia and the outer coats of the media with relatively little actual weakening of the intima, in spite of its altered appearance. Thus herniation of the inner coats through the diseased outer ones, with the formation of a saccular aneurysm, is the common thing in syphilis of the aorta, while a rupture of the diseased inner coats and a dissection inside of the healthy outer coats occurs in atherosclerosis.

With this background of increased blood pressure and arterial disease is almost always associated an immediate precipitating factor further to elevate the blood pressure.

Physical trauma is commonly given as the precipitating factor, but, as Shennan has pointed out, a severe blow to the chest or the abdomen would be more likely to lead to immediate rupture of the aorta.

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Shennan suggests that in many cases the precipitating factor is "internal trauma," such as straining, undue emotion, etc., which may raise the blood pressure sufficiently to begin dissection in an aorta whose media is already diseased. In a case reported by White and his associates,<sup>8</sup> a lawyer trying a case in court was suddenly seized with agonizing pain. Other cases have occurred in patients with prostatic obstruction as they attempted to urinate or in patients during an epileptic convulsion. It is conceded that none of these circumstances can so raise the blood pressure that rupture of the intima of a normal aorta can occur.

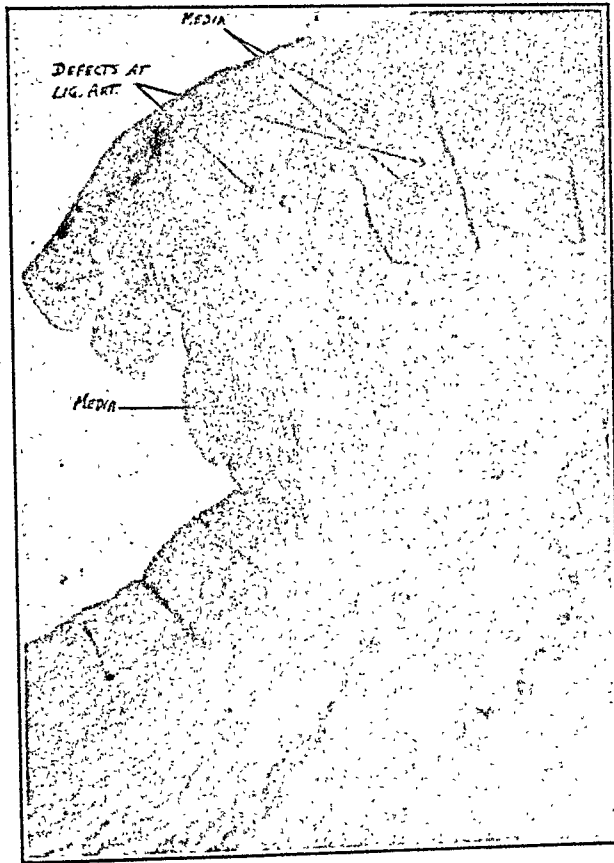


Fig. 1.—Longitudinal section of normal aorta at ligamentum arteriosum. Note fibrous band passing through media toward intima, and spreading out between fibers of media. This natural defect tends to weaken the aorta at this point. ( $\times 52$ .)

#### SITE OF RUPTURE

Contrary to what would seem to be the case, the original rupture commonly does not occur in immediate relation to an atheromatous plaque or ulcer. Of the fifteen cases examined personally by Shennan, only four showed an immediate relation to atheromatous patches, and none was in the base of an atheromatous ulcer. Instead, the site of rupture appears to be determined by mechanical factors which tend to submit the aorta to particular strain at certain points. In Shennan's collected cases, most of the intimal tears were either in the ascending arch of the aorta or at the site of the ligamentum arteriosum. Shennan believes that "... when the aortic valves have closed, the abrupt recoil of diastole must bring about a longitudinal stretching of the ascending aorta, and



must forcibly drive the aortic valve, along with the origin of the aorta, downward and away from the transverse part." Hence, the intimal tears in the ascending aorta are usually transverse. On the other hand, "... at the ligamentum one passes from the relatively free arch to the relatively fixed descending aorta, and ... at every pulsation there is a hingelike motion at the junction of the two. This implies a local enhanced tendency to wear and tear, and to degeneration of the wall."

From the study of several aortas that were thought to be normal both grossly and microscopically, it is apparent that the aortic wall at the insertion of the ligamentum arteriosum is weaker than elsewhere. This is anticipated when it is recalled that the old ductus arteriosus must be obliterated, a process which necessarily requires fibrous tissue replacement. At the site of passage of this band through the walls of the aorta, a dimpling of the intima of the aorta can almost always be made out grossly, and microscopically a band of fibrous tissue passes from this dimple through the coats of the aorta, tending to spread out in the deeper reaches of the media (Fig. 1). While this is probably the important reason for the predominance of dissecting aneurysms at this point, it is probable that the fixation of the aorta at this point is also a factor.

#### CHANGES IN THE AORTIC WALL LEADING TO DISSECTION

Of the specific changes in the aortic wall that precede dissection, it is probable that degeneration and inflammation may both play a part in different cases. Those cases associated with atherosclerosis are usually of a degenerative nature. Shennan has pointed out that "deleterious agencies," acting to produce degeneration of the aorta, would be more likely to affect the innermost layers of the media than the other portions, because of their poorer blood supply. Microscopically the lesion consists of the various changes commonly noted in the intima in atherosclerosis (i.e., fatty deposits, hyalinization, calcification) plus rather characteristic medial changes. The regular parallel arrangement of the muscular and elastic laminae is irregularly interrupted by fibrous tissue, which often appears hyaline and degenerated. This tissue runs obliquely or transversely in the media. Occasionally a vas vasorum will be noted in close relation to the fibrous fault, and occasionally this small vessel will show evidence of intimal proliferation, with narrowing of its lumen. In such cases it is probable that the fibrous tissue in the media represents an area of insufficient blood supply. In other cases no disease of the vasa can be made out, and then the medial change is indefinitely assigned to toxic or metabolic causes. Occasionally small areas of necrosis are noted in the media in cases of atherosclerosis; these are usually crescentic in shape, contain a number of polymorphonuclear and round cells, but lack other evidences of inflammation. Usually these areas appear to be a result of infarction of the aortic wall, from obliterated vasa vasorum.

In the reported cases in which inflammation (and not primary degeneration) is thought to be the important agent, syphilis is the commonest inflammatory process. In 218 cases of recent dissection collected by Shennan, syphilitic mesaortitis was thought to be present in 21. In the Roper Hospital, where negro patients have a high syphilis rate, it appears that syphilitic mesaortitis is more commonly the background for dissection than Shennan's figures would indicate. Of the five well-developed dissections reported here, one was definitely syphilitic and an-

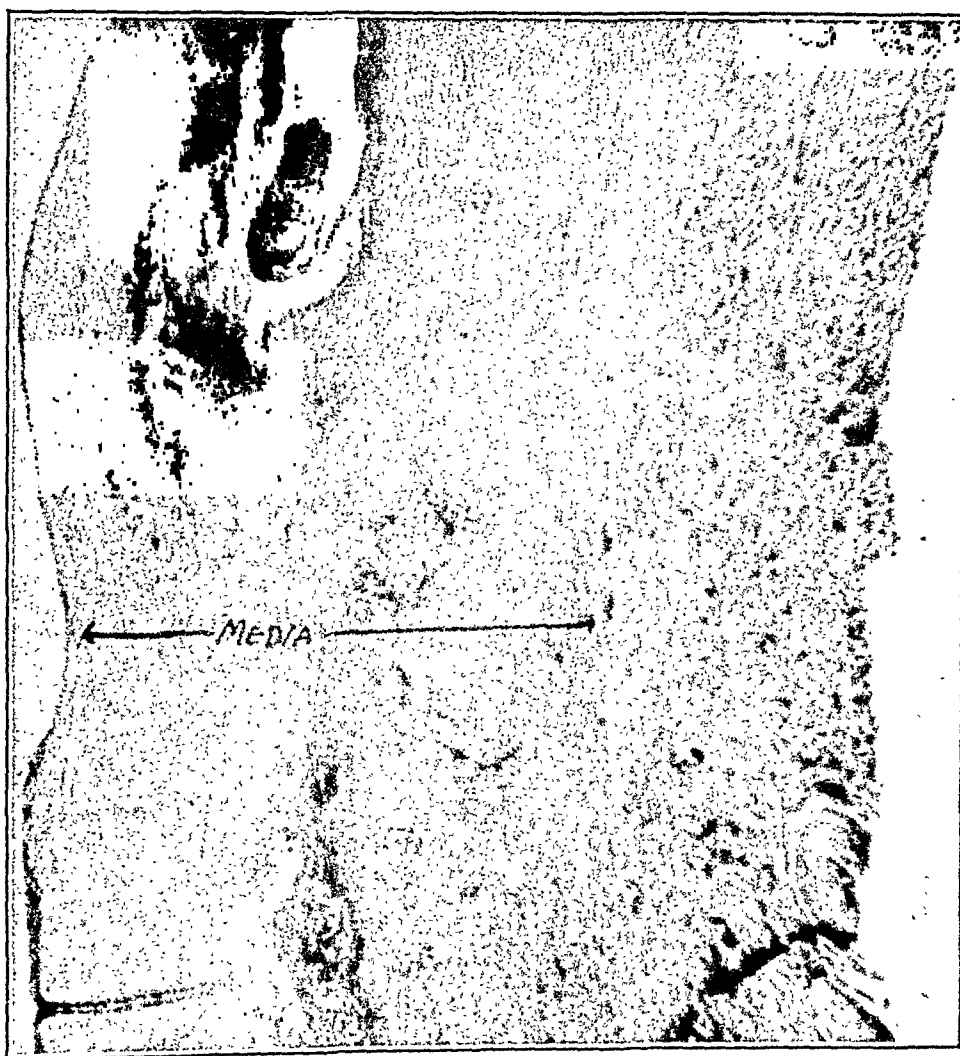


Fig. 2.—Case 27730. Medial necrosis of aorta in syphilis. Such a lesion as this probably exists when syphilitic aortitis is the background for dissection, rather than the usual scarring of the outer coats of the media. ( $\times 20$ .)

other may have been of that nature. There are several other sections of syphilitic aortas in our files in which short dissections have occurred, and others in which it would be very easy to imagine that a dissection could take place. Two of these deserve description.

CASE 27730:35-100, a sixty-year-old negro male, dying of cardiac decompensation. The aorta was irregularly dilated, especially about the orifice of the innominate artery, where there was a small funnel-shaped aneurysm. Grossly the intima was very roughened and nodular, and the adventitia shared in the general thickening of the walls. Microscopically, the adventitia and media showed large perivascular collec-

tions of lymphocytes, and the adventitia was greatly thickened and hyaline. Much more striking were several crescentic areas of necrosis in the innermost layers of the media, where muscle and elastic tissue were disintegrated and many polymorphonuclear cells were collected (Fig. 2). The defects thus formed extended transversely about the aortic wall, and gave the appearance of crescentic abscesses between the intact fibers of the media. There was no evidence of hemorrhage. A small amount of calcification was noted about the necrotic area. The overlying intima was not calcified, although somewhat thickened and hyaline. This was judged to be a syphilitic aorta, with acute necrosis; the blood Wassermann reaction was four-plus.

Another aorta, that of a fifty-year-old negress (28462:35-113), showed even more striking changes. Grossly the aorta showed the nodular and striated thickening of the intima about the commissures of the aortic valves, with valvular insufficiency, commonly associated with syphilitic aortitis. Microscopically it was evident that a



Fig. 3.—Case 28462. Extensive medial necrosis of aorta, with small dissection. This section shows evidences of syphilitic aortitis. Note narrowing of vas vasorum in adventitia. ( $\times 12$ .)

small dissection had occurred in the walls (Fig. 3). The media was extensively distorted by bands of fibrous tissue running obliquely and transversely to the normal muscular and elastic laminae. In several fields, these fibrous bands extended up to and involved the intima. Within one of these fibrous bands an old area of hemorrhage was noted. The periphery of the dissecting area showed a granular deposit of calcium. There was no evidence of the formation of an endothelial lining about the clot. Deeper in the media, and in the adventitia, were large collections of lymphocytes and plasma cells, usually in a perivascular position, and being so closely packed as to suggest miliary gummas. The blood Wassermann reaction was four-plus.

From a study of these two aortas, one with a very small old dissection, the other without dissection but certainly prone to it, it appears that

mesaortitis can cause dissecting aneurysm. However, the distortion of the muscular and elastic laminae of the media that occurs in the common form of syphilitic mesaortitis probably resists the splitting of the media necessary for dissection, as has been pointed out by Gager<sup>3</sup> and by Shennan. If dissection should begin, it seems doubtful that it would extend far along the aorta. Further, it seems likely that when the aortic disease associated with dissecting aneurysm is syphilitic, there must be medial degeneration and necrosis similar to that seen in dissecting aneurysms whose background is atherosclerosis.

A discussion of the factors leading to dissection would be incomplete without reference to the work of Babes and Mironescu.<sup>1</sup> In 1910 they stated that, while increased blood pressure usually causes intimal changes, it may cause degenerations of the media with breaks in that coat. Quoting: "These medial splits are certainly usually a direct consequence of the dilatation [of the aorta] and accordingly take place perpendicularly to the surface of the aortic wall, but the degeneration of the media may, in consequence of dilatation of the inner components of the wall, lead to splittings of the layers parallel to the surface of the aortic wall. . . . Then after the degenerated intima had burst as a result of trauma, the blood was poured between the already split medial layers." However, it would seem very unlikely that the inner coats of the aorta could dilate without the outer coats dilating to a proportionate extent. Consequently it would appear that such a force, acting on the inner coats to produce perpendicular tears, would act on the outer coats in the same way, giving a direct rupture without a dissecting split in the media.

#### SYMPTOMS

The usual symptom of onset is a sudden intense pain in the thorax, frequently knifelike in character, and generally radiating to the back or shoulders. A sensation as of suffocation commonly comes on early and may be followed by collapse or even coma. The blood pressure usually remains elevated, as contrasted with the fall usually encountered in coronary occlusion. A change in the character of the pain, or an extension of the pain, as down an extremity or to the abdomen, suggests that dissection is progressing in the direction indicated by the new radiation of pain. The usual symptoms of mediastinal compression, such as difficulty in swallowing, inequality of the pupils, etc., may be present. When extension occurs along the iliac or brachial arteries, with resultant narrowing of the lumina of these vessels, cyanosis, coldness, loss of pulse or numbness may develop, as in the case of Kellogg and Heald.<sup>4</sup> Such a state of affairs, occurring suddenly and associated with pain in one with hypertension, will occasionally permit the diagnosis to be made ante mortem, as pointed out by Crowell.<sup>2</sup> Other less common symptoms may be blindness, hemiplegia, etc., and when these are present, extension has usually occurred along the carotids.

Very rarely has the diagnosis been made during life, and none of the cases here reported was so diagnosed.

#### "HEALING" OF DISSECTING ANEURYSMS

While it is generally thought that the condition is always fatal, such is not the case. Kellogg and Heald state that 80 per cent die within a few days, but that the remaining 20 per cent have a good chance of recovery. If external rupture of the dissecting channel does not occur, with hemorrhage into the body cavities, it is easy to conceive that recovery can take place. All but one of the collected cases of recovery from the initial dissection showed two ruptures, one from the aortic lumen into the walls, and another from this new channel back into the lumen of the aorta. When such a rupture has not occurred, there is further extension of the dissection with each systole and imminent danger of rupture to the exterior. This danger is much greater, of course, if the blood pressure remains at the level at which the original rupture and dissection occurred. If rupture back into the lumen of the vessel occurs, and the blood pressure is kept at a low level, the new channel may become coated with endothelium, and, while it is by no means a perfect vessel, it will function. Evidence of healing of dissecting aneurysms is found in those cases where old channels, lined by endothelium, are found within the walls of the aorta. Seventy-four such cases have been found by Shennan in the literature, and another is added in this report. Of the 74 cases collected by Shennan in which healing had occurred, many were thought to be several years old. Samson's case<sup>6</sup> was thought to be of five years' duration. The case included briefly in this report (and reported more completely elsewhere<sup>6</sup>) is thought to have been of fifteen and one-half months' duration. In such cases, death is usually from cardiac failure, chronic nephritis, or intercurrent infection.

#### CASE REPORTS

CASE 1 (56:14-11).—R. B., a twenty-two-year-old negress, was first admitted to the Roper Hospital on Dec. 16, 1913, and discharged Dec. 30, 1913. She was re-admitted on Jan. 29, 1914, and died Jan. 31, 1914.

The charts give little information. The first admission was apparently for a gynecologic condition. The blood pressure was not recorded. On the second admission she was complaining of severe pain in the epigastrium, which was only slightly relieved by large doses of morphine. The temperature was subnormal, the pulse rate 120 per minute, respirations 22 to 36 per minute. The blood pressure was not recorded. She died soon after admission.

Autopsy was performed a few hours after death, and the heart and aorta were preserved in the Pathological Museum. Examination of the mounted specimen showed a moderately enlarged heart, weighing about 500 gm. The coronary arteries were normal. The myocardium of the left ventricle measured 1.75 cm. in thickness. The valves were normal. The intima of the aorta showed a number of rounded, raised plaques, chiefly about the mouths of the small vessels. Most of these plaques were hyaline, but a few were calcified. There was considerable wrinkling of the intima, especially between plaques that were near each other.

At the orifice of the innominate artery there was a small saclike pouching of the walls, but the intima here appeared the same as elsewhere. At the beginning of the descending aorta, and corresponding to the site of attachment of the obliterated ductus arteriosus, there was a crescentic tear in the intima (Fig. 4). This began as a longitudinal rent proximally, passing across a depressed area in the intima (which was the remnant of the aortic end of the ductus), and then bent in a uniform arch to end as a transverse tear across the most inferior and most concave portion of the arch, partially surrounding at this point a small hyaline plaque. The whole tear was about 2.5 cm. in length. At the middle of this crescentic tear there was

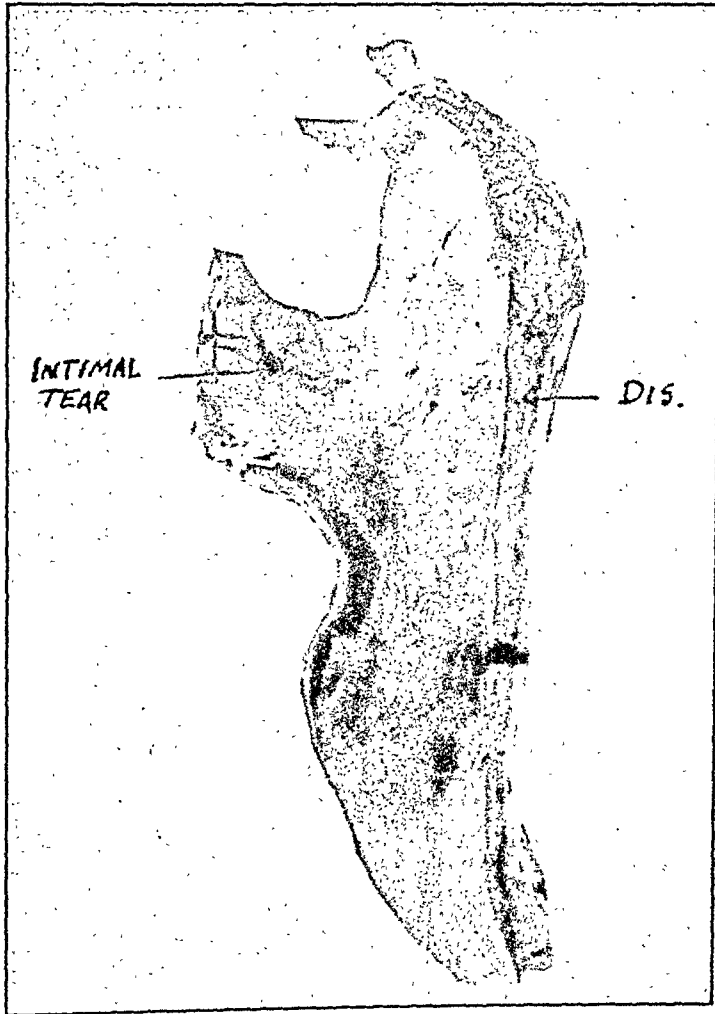


Fig. 4.—Case 1. Descending portion of thoracic aorta, showing intimal tear and dissection between layers of media.

another which crossed the first at a slight angle; this appeared to be a secondary tear, and was about 2 cm. in length, the point of intersection exactly overlying the intimal depression mentioned above. Beneath this, the media was separated into two layers, the separation appearing grossly to be between the middle and outer thirds of the muscle coat. Between these layers a strikingly uniform blood clot completely surrounded the aorta, and was generally about 0.5 cm. in thickness. The dissection extended proximally for about 2 cm. and distally as far as the specimen extended. (The description written at that time stated that the dissection extended to the diaphragm.) The adventitia was somewhat thickened in a uniform fashion. Posteriorly, at a point about 5 cm. distal to the intimal tear, the dissection was about 2 cm. thick, and the extravasation extended into the adventitia and nearby structures, beneath the pleura over the roots of both lungs. At this

thickest point there was a large ragged ruptured area where the dissecting sac communicated with the pleural cavity, where the fatal hemorrhage occurred.

Sections from the aorta at the site of the dissection show a somewhat thickened hyaline intima, and a greatly damaged media. Muscle and elastic tissue fibers are interrupted several times in each low-powered field by infiltrating fibroblasts, and the fragments of muscle are hyaline and degenerated.

Numerous lymphocytes and plasma cells are seen at a little distance from the dissected area, which, with the numerous fibroblasts, indicate that the patient lived for some little time after the dissection began. Most of these cellular changes are taken to be secondary to the dissection rather than the pathologic background for the dissection. Sections from the arch proximal to the dissection show prominent but small slitlike channels that are taken to be dilated lymphatics. They are in close proximity to the vasa vasorum and are lined with endothelial cells. About these small channels and about the vasa vasorum are numerous plasma cells and lymphocytes, occurring in small clusters in which fragments of a collagen-like material are frequently found. Other portions of the media do not show these slitlike spaces, but localized areas of fibrosis, extending both parallel to, and across, the regular fibers. Intimal changes away from the dissection are not prominent, there being merely a mild degree of hyalinization, without fatty deposits or calcification. This lack of evidence of atherosclerosis, together with the youthfulness of the patient (twenty-two years), makes rheumatic aortitis a possibility, although Aschoff bodies cannot be demonstrated in the myocardium and although the valves are free from disease. In some areas the changes are such as are commonly found in syphilitic aortitis. At any rate, it appears that the medial disease in this case is more of an inflammatory nature than a primarily degenerative one.

CASE 2 (12397:31-125).—P. M., a forty-nine-year-old negro, a laborer, was admitted to the Roper Hospital on May 7, 1931, and died on May 19, 1931. Symptoms of congestive heart failure had been present for six months, growing progressively more severe.

He had a penile sore in 1917 and a "stroke" in 1930, but the effect of the latter had been only temporary. There had been no other illnesses.

On examination his temperature was 98.4° F., pulse rate 114 per minute, respirations 28. The blood pressure was 216/140. Chest examination showed scattered râles over the bases of both lungs, but no other abnormalities. The mediastinum was normal on percussion. The apex was noted by auscultation to be in the sixth interspace, just to the left of the nipple line. Both the aortic and the pulmonic sounds were accentuated, but the other sounds were normal and there were no murmurs. The radial arteries felt thickened. The pulse was regular. The Kolmer and Kahn tests of the blood were negative.

On digitalis therapy, moderate restriction of fluid intake, and diuretics, there was definite improvement, with disappearance of the edema and with much less dyspnea. On May 18 he was suddenly seized with a severe pain in the left side of the chest, markedly exaggerated by deep breathing. Simultaneously the pulse rate dropped to 48 per minute, and dyspnea became severe. A quarter grain of morphine relieved the pain somewhat, and the patient dropped off to sleep (or passed into coma?), although he groaned continuously. The skin became cold and clammy, the pulse rate remained slow and became irregular, and he died fourteen hours after the onset of the pain. The temperature was subnormal for several hours before death.

Autopsy was performed the day after death. The heart weighed 600 gm. and the left ventricle was markedly hypertrophied. There was a slight pericardial effusion, without evidence of bleeding into the sac. The lungs and liver were con-

gested. The intima of the aorta was irregularly thickened, rough and hyaline, and was moderately dilated in the ascending portion of the arch. Three transverse linear breaks resembling incisions were noted in the descending portion of the arch, and one of these communicated with a longitudinal sac in the wall, which had its base on the pulmonary artery, and contained a fresh thrombus. Unfortunately the specimen was not more fully described in the records and was not preserved. The description sounded like a rather small dissection, which probably occurred at the time of the onset of the severe pain in the side. As it had not ruptured, it probably would not have been fatal if the patient had not already been in poor condition.

Microscopic sections from the aorta show an irregularly nodular intima, the nodules composed of a loose, myxomatous fibrous tissue in which numerous small fat droplets are evident. Deeper in the media irregular breaks are noted, confined to the inner two-thirds of the media, in which the medial fibers are completely dis-

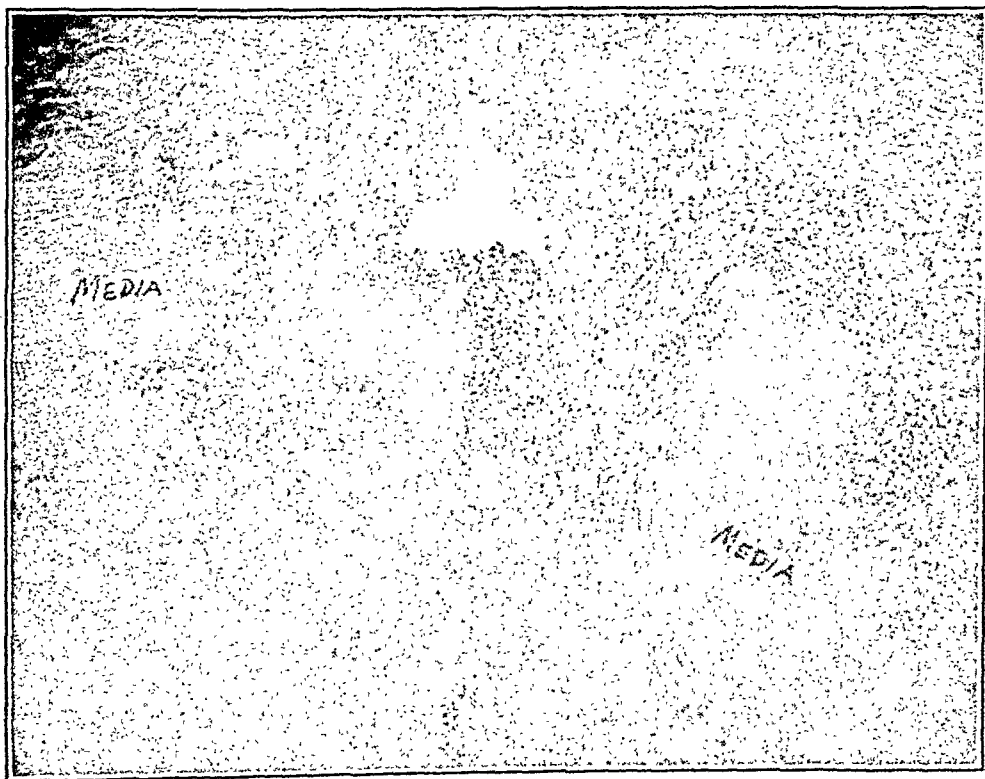


Fig. 5.—Case 2. Marked medial necrosis, with complete disruption of muscular and elastic fibers. Not from the area of dissection. This aorta showed unmistakable evidence of syphilis. (X 80.)

rupted. The ends of the muscular and elastic fibers are frayed out and hyaline. One of these faults occupies almost the whole of a low power microscopic field and is filled with a loose, fragile-looking, young fibrous tissue in which are large numbers of mononuclear and polymorphonuclear cells (Fig. 5). The outer layers of the media, even at this point of greatest involvement, appear quite normal, and their muscular and elastic fibers pursue their normal circular course. Elsewhere in the media smaller cellular accumulations are noted, composed of mononuclear and plasma cells confined to small areas about vasa vasorum and having the appearance in some areas of miliary gummata. While the sections at hand now do not include the dissection proper, it is believed that dissection occurred through a lesion similar to the large one described above, the intimal covering of which appeared very delicate. This aorta appears to be definitely syphilitic.

CASE 3 (21487:34-110).—A. W., a negro male of thirty-three years, was first admitted to the Roper Hospital in June, 1922. A high thigh amputation was done



for a ruptured aneurysm of the femoral artery, the nature of which is not clear from the record. There was no history of trauma. The blood pressure was 190/120.

On his final admission to Roper Hospital, on May 23, 1934, he was forty-five years old. His symptoms were those of congestive heart failure of about four months' duration. He had had a sore on his penis many years before.

On examination, the heart was greatly enlarged, and the second aortic sound was loud and ringing. The arteries were palpably thickened, and the blood pressure was 220/170. Pulmonary congestion, a large tender liver, ascites, and edema were noted. The respirations were 28 per minute. The urine showed a specific gravity of 1.022, a heavy trace of albumin, occasional hyaline casts, and occasional

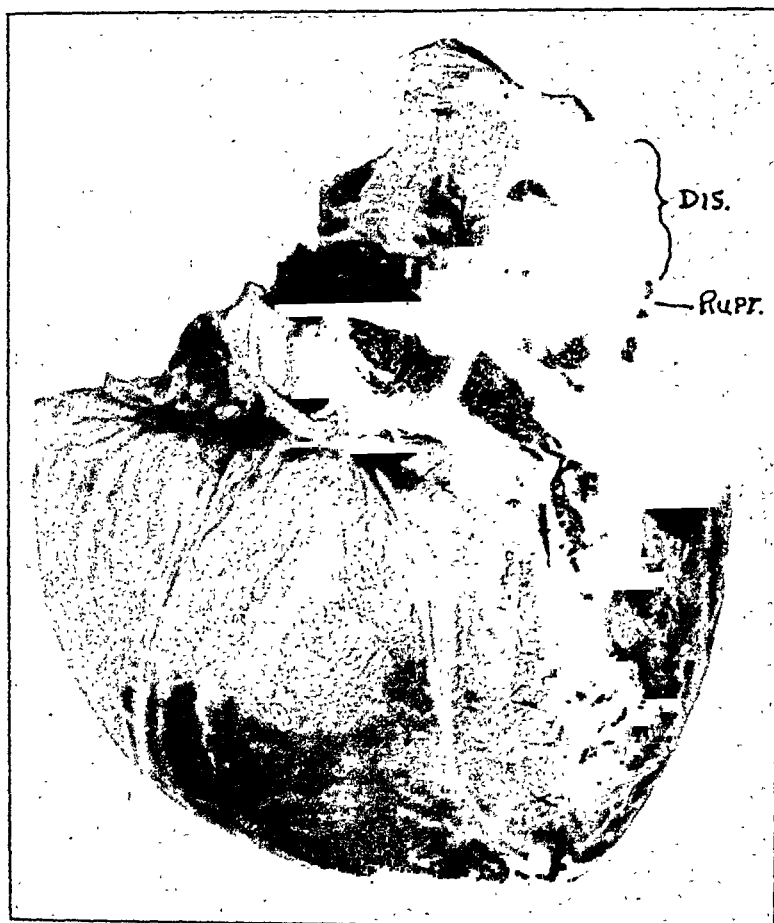


FIG. 6.—Case 3. Small dissection of ascending aorta, with rupture into pericardium. Viewed from outer surface of aorta.

red and white blood cells. At no time did he complain of pain, only of dyspnea and a general feeling of discomfort. No improvement was effected by sedation, diuretics, and digitalis. On May 31, 1934, without an outcry, he suddenly slumped back in bed, became pulseless, and ceased to breathe.

Autopsy was performed forty-eight hours after death. There was moderate edema of the left leg. The pleural sacs were dry. The lungs showed merely passive congestion. The pericardial sac contained a large blood clot estimated to represent about 1,500 c.c. of blood. The heart was greatly enlarged, weighing 960 gm., and was very pale. The myocardium of the left ventricle was 2.5 to 3.0 cm. in thickness. The mitral, tricuspid, and pulmonary valves all appeared normal. Beginning just above the aortic cusps on the anterior surface, the intima was irregularly elevated

and small deposits of fat were noted, but no definitely calcified plaques could be found. A little higher up in the ascending aorta definite longitudinal wrinkling of the intima was noted with numerous hyaline nodules. The adventitia was also definitely thickened. In the upper portion of the part showing the atheroma and extending upward to the part that appeared grossly to be syphilitic, there was a linear opening in the intima 3 cm. in length. This was on the anterior surface and was curved so as to form a barely evident "S". In its center it gaped about 0.5 cm., and at its upper end it showed a double split, forming a "Y," each limb of which was very short. This tear extended into the media, dissecting there in a circular fashion so as almost to surround the aorta, and extending downward along the right coronary artery for a short distance. The dissection continued distally for about 3 cm., lying in the very outer coats of the media (Fig. 6). Near the

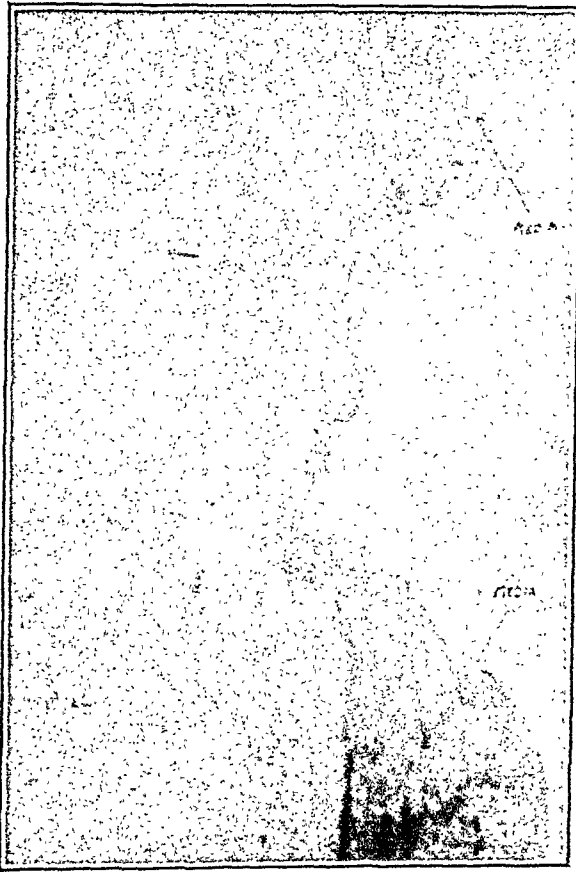


Fig. 7.—Case 3. Complete disruption of media in atherosclerosis. Note marked narrowing of vasa vasorum. (This defect was one of several; it was not the site of the fatal dissection.) ( $\times 18$ ).

center of the dissected area, and corresponding to the most gaping portion of the tear in the intima, this tear extended through all the coats of the aorta. The opening through the adventitia was about 4 mm. in diameter, and its edges were rough and gaping. It was this extension of the tear that gave rise to the hemopericardium and the sudden death. At the same level as this large tear, but on the right side of the aorta, there was a roughly V-shaped tear, apparently in the media only, and covered over by a thin layer of intima. The angle of the "V" was directed upward and to the right, and the limbs extended downward between the commissures of the right posterior cusp of the aortic valve. In the region of this V-shaped fault there was no evidence of dissection, either recent or old.

Sections through the aorta at the site of the dissection show large defects in the media, where the normal circular muscle bands are replaced by hyaline or necrotic whorls of tissue. Hemorrhage has occurred into the media at the site of

this fault, and dissection is evident even between the layers of media that appear normal. The intima overlying the defect is somewhat thickened and hyaline, but by no means elevated to form a plaque and there is no evidence of calcification. A little to one side of the actual medial defect the intima is broken through, and the blood was apparently admitted to the medial defect from this intimal cleft. There are a few cells in the line of cleavage, and in the outer layers of the media and in the adventitia are larger collections of cells. These latter cells are largely fibroblasts with a small spattering of lymphocytes among them. The round cells do not appear to have a definite perivascular arrangement, and there are none of the plasma cells so commonly seen in syphilitic aortitis (Fig. 7).

This case showed gross features in the aorta very strongly suggestive of syphilis as well as of atherosclerosis, but the microscopic appearance is that of an aorta degenerated from atherosclerosis. The aneurysm of the femoral artery in this case, rupturing in 1922, may have been a dissecting aneurysm, but that cannot be definitely stated. At autopsy there was a widespread atherosclerosis in all the larger arteries.

CASE 4 (21990:34-127).—(This case is reported in more detail elsewhere.) J. F., a negress, was first seen at the age of forty-six years in the Shirras Dispensary. At this time (1927) the blood pressure was 220/130. She was admitted to the Roper Hospital on March 17, 1933, complaining of severe pain in the epigastrium, radiating through to the back, which had come on suddenly about eight hours before. Vomiting, slight hemoptysis, and definite hematuria came on a few hours later.

On examination she was in acute distress. The temperature was subnormal, pulse 90 per minute, respirations 24, blood pressure 190/110. The apex beat was in the fifth interspace 2.5 cm. to the left of the midclavicular line. The heart tones were normal, and no murmurs were heard. The arteries were markedly sclerotic. There was marked tenderness in the epigastric region and in both lumbar regions, with moderate tenderness in the suprapubic area. The voice was quite hoarse. On laryngoscopic examination a partial paralysis of the right vocal cord was noted, with imperfect approximation. A few hours after admission the urea nitrogen was 21 mg. per 100 c.c., and this gradually rose to a peak of 121 mg. four days after admission, after which it gradually fell to 13 mg. on the day of discharge. The urine contained grossly evident blood for five days after admission. Leucocytes on the night of admission numbered 28,100, with 79 per cent polymorphonuclears. The hemoglobin was 85 per cent (Dare). The leucocytes gradually fell to 7,600 with 65 per cent polymorphonuclears on the day of discharge, the hemoglobin then being 50 per cent (Dare). The blood Kolmer and Kline tests were negative. The temperature rose to 101.4° F. on the day after admission, gradually falling to normal after one week. The pulse varied below 130, being highest on the second day after admission, and gradually tending to fall to normal. The blood pressure was constantly elevated, although subject to variations. An x-ray of the chest two weeks after admission showed "an unusually large aneurysm of the entire aortic arch," without noteworthy cardiac enlargement.

Morphine was required for the relief of pain for several days, but improvement was constant, and at the time of discharge forty-two days after admission the only complaints were pain, weakness, and numbness in the right foot and leg.

On June 25, 1934, J. F. was readmitted to the hospital, complaining of shortness of breath, and difficulty in swallowing, talking and breathing. The blood pressure was 192/140. Coarse moist râles were heard over both lung fields. The heart was markedly enlarged and the sounds were of fair quality. A loud, high pitched systolic murmur was heard, of maximum intensity at the aortic area and at the apex. There was a tambourlike second aortic sound. The abdomen was negative. Moderate edema of both feet was noted, especially the left. An x-ray plate of the chest, taken the day after admission, showed little if any change in the appearance of the

"aortic aneurysm," although the heart had enlarged greatly in the interim, now measuring over 7 inches as compared with 5 inches in April, 1933.

The urine contained 3-plus albumin but no casts. The hemoglobin was 62 per cent (Dare). The blood K  lmer and Kline tests were negative. She showed little improvement, gradually became stuporous, and died on July 1, 1934.

Autopsy was made twenty-four hours after death. There was marked nephrosclerosis and a large old infarct of the left kidney. Cardiac hypertrophy was moderately advanced, and there were evidences of congestive heart failure. The coronary arteries were patent and appeared normal. Lobular pneumonia was present.

Viewed from the exterior, the aorta showed a rather uniform dilatation beginning in the distal portion of the arch and extending to the termination of the aorta. On opening the aorta the true aortic channel was almost completely surrounded by a second vessel, crescentic in shape, which also contained blood. This false channel extended proximally into the descending portion of the aortic arch, while distally it went well out into both iliac arteries. The true nature of the condition was not realized at the time of autopsy and the lower extent of the dissection was not determined; it extended more than 6 cm. from the bifurcation, where both iliacs were severed. The communication between the two channels and the site of the rupture, which apparently occurred fifteen and one-half months before, was at the termination of the ligamentum arteriosum. The orifice connecting the two channels was a slightly gaping, slitlike one, 1.5 cm. in length, its direction almost transverse, but with its posterior end directed slightly downward. Proximal to the dissection, the intima showed merely a few fatty deposits, and no calcification or ulceration. There was no abnormal thickening or wrinkling of the intima or adventitia. There was no grossly evident lesion of the intima near the site of rupture. The intima of the false channel was irregularly roughened and wrinkled. Generally the lining was paler than that of the true channel, but a few small fatty deposits were noted in the false channel. The false vessel surrounded the true one except on the posterior surface where the two walls merged. Numerous intercostal arteries were torn across by the false channel. The renal, the pancreatic, and the superior mesenteric arteries showed false channels in their walls, continuous with the channel in the walls of the aorta, and they also contained blood. Thrombi were noted in the lumen of several of these secondary false vessels, and these thrombi extended into the false aortic channel to surround the orifices of these smaller vessels.

Sections from the area of dissection show that the false vessel lies between the middle and the outer thirds of the media. The media, as included in the walls of both channels, is extensively degenerated, and the elastic tissue is fragmented and quite scarce. The intima of the new channel is very dense and thick, the media thin and apparently inefficient, the adventitia greatly thickened.

Sections taken from the aorta proximal to the splitting of its walls show numerous "faults" in the media, interrupting the normal circular fibers and tending to spread out somewhat between the layers of the media. At these faults the muscle is degenerated and the elastic tissue has completely disappeared, leaving in its place a loose, hyaline fibrous tissue containing a number of endothelial cells lining small sinuses, apparently of lymphatic nature. This tissue gives the appearance of being quite fragile. In no section is there any suspicion of syphilitic disease. As a matter of fact, atherosclerosis is also at a minimum, as there seems to be little intimal degeneration even where medial defects are quite prominent.

CASE 5 (24781:35-9).—T. G., a negro of about forty years of age, was not admitted to the hospital, and hence his history is far from complete. It was learned that he had had a heated argument with his wife, after which he left the house in a fit of rage. As he passed through the yard, he suddenly fell and in a few minutes was dead. Because of the unusual circumstances about the case, the wife refused to

answer questions about her husband's state of health, thinking that she was to be prosecuted for his death. But, curiously enough, the wife requested an autopsy.

Autopsy was performed the day after death (Jan. 13, 1935). Opening the thorax revealed that the left pleural cavity contained about 3,000 c.c. of partially clotted blood. The heart and entire aorta weighed 435 gm. The heart itself was entirely normal. The ascending portion of the aorta was smooth and elastic and quite resistant to tearing. In the transverse portion of the arch, adjacent to the orifices of the great arteries, several atheromatous plaques were noted in the intima, yellow and fatty at their periphery, hyaline toward their center, with a minimal amount of calcification. Just lateral to the origins of the first and second left intercostals, about 2 cm. from the termination of the ligamentum arteriosum, was an

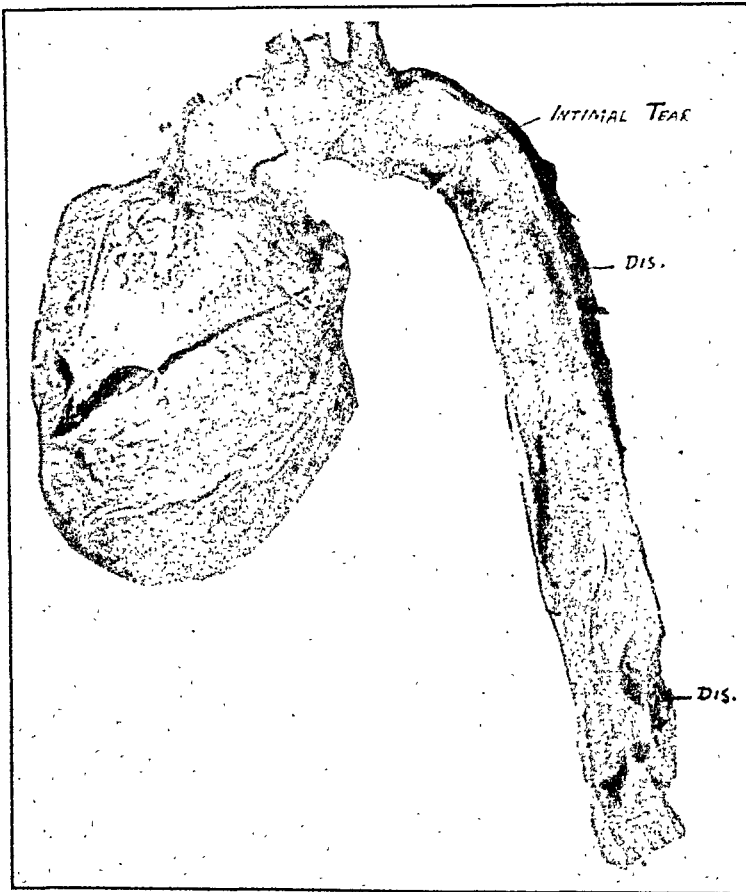


Fig. 8.—Case 5. Intimal rupture just to one side of a small atheromatous plaque, with dissection in the adventitia, and rupture into the left pleural sac.

intimal plaque about 7 mm. in diameter, with very slight calcification. At its left border this plaque was elevated and torn, giving a V-shaped tear in the intima, and it was through this that rupture occurred. Arising at this site and extending in both directions in the axis of the aorta was a blood clot which grossly appeared to lie between the media and the adventitia (Fig. 5). At its origin the clot was 4 mm. in thickness and completely enveloped the aorta, although it was much thinner opposite the rupture. Proximally the dissection extended as far as the reflection of the pericardium, where it abruptly terminated. Dissection continued along the great arteries arising from the arch, especially the left subclavian, for a distance of several centimeters. Distally the dissection completely enveloped the aorta as far as the origin of the celiac axis, where it was 1 mm. thick. Just beyond this, the

dissection ended in an irregular margin. The point of rupture of the dissecting sac was just over the rupture in the intima. Here the adventitia was definitely torn, and the edge of the sclerotic plaque in the intima protruded through the adventitial opening. (Doubtless, in such a case as this, where a very thin-walled sac is formed, only a very short interval exists between the time of the beginning of the dissection and the rupture of the dissecting sac.)

Microscopic sections from this aorta show that the intima is only slightly thickened and somewhat hyaline, with a finely granular deposit of calcareous material scattered about, but with few definite calcareous plaques formed. In most areas the media appears entirely normal. In several areas, however, the muscle fibers are definitely degenerated and the elastica has lost its regular arrangement. The adventitia is normal both in thickness and general appearance. The dissection is largely in the adventitia, between its component layers: in some sections the separation is between the media and adventitia, but in no field is the media itself split. There is no suspicion of syphilitic disease.

#### COMMENT

From the data at hand, a few things can be gleaned that may be of assistance in the clinical management of a case in which the diagnosis can be made during life. In the event of a recent dissection, it would seem essential to lower the blood pressure, preferably by venesection followed by agents which may act over a longer period of time. This may serve to arrest further dissection. It goes without saying that absolute rest is all-important, as the danger of complete rupture remains grave for many days after beginning dissection.

In the event that the patient recovers from the period of actual dissection, it is probable that he will be handicapped by the loss of aortic elasticity, thus throwing upon the heart the entire burden of propulsion of the column of blood. This is evidenced by the rapid development of signs of decompensation in Case 4, following establishment of the new channel. Further, as the "healed" channel is still prone to complete rupture due to imperfections in its walls, the patient is not out of danger even when he has survived active dissection. With this in view, a patient who has recovered from his dissection must be handled in the same way as any cardiac cripple.

#### REFERENCES

1. Babes, V., and Mironescu, T.: Ueber dissezierende Arteriitis und Aneurysma dissecans, *Beitr. z. path. Anat. u. z. allg. Path.* 48: 221, 1910.
2. Crowell, P. D.: Dissecting Aneurysms of the Aorta, *J. A. M. A.* 77: 2114, 1921.
3. Gager, L. T.: Dissecting Aneurysm of the Aorta Complicating Hypertension, *AM. HEART J.* 3: 489, 1928.
4. Kellogg, F., and Heald, A. H.: Dissecting Aneurysm of the Aorta, *J. A. M. A.* 100: 1157, 1933.
5. Peery, T. M.: "Healed" Dissecting Aneurysm of the Aorta, *Arch. Path.* 21: 674, 1936.
6. Samson, P. C.: Dissecting Aneurysms of Aorta, Including Traumatic Type, *Ann. Int. Med.* 5: 117, 1931.
7. Shennan, T.: Dissecting Aneurysms, Medical Research Council Special Report Series, No. 193, London, 1934, His Majesty's Stationery Office.
8. White, P. D., Badger, T. L., and Castleman, B.: Dissecting Aortic Aneurysm Wrongly Diagnosed Coronary Thrombosis, *J. A. M. A.* 103: 1135, 1934.

# THE SIGNIFICANCE OF AN UPRIGHT OR DIPHASIC T-WAVE IN LEAD IV WHEN IT IS THE ONLY DEFINITE ABNORMALITY IN THE ADULT ELECTROCARDIOGRAM\*

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SINCE the value of chest leads in the study of coronary occlusion was demonstrated in 1932,<sup>1</sup> many observations have been made concerning them, and their advantages and limitations have become more clearly defined. In a certain group of cases the limb leads furnish all or practically all the diagnostic information. Lead IV shows no deviation from normal. Examples of this are seen in many cases of healed posterior infarction. In another group of cases abnormalities are found in both the limb leads and Lead IV. In this group the findings in Lead IV may be (a) superfluous (b) of considerable assistance in clarifying or intensifying a diagnostic impression gained from limb leads, or (c) of primary importance. In a third group Lead IV shows significant abnormalities, when the limb leads are normal. For purposes of evaluating the benefits to be derived from taking chest leads, careful study of this third group seems indicated. The question is: If an abnormality appears in Lead IV when limb leads are normal, is it significant of heart disease or is it misleading?

The present paper is based on a group of twenty-six adult cases in which the T-wave in Lead IV was upright, or diphasic with a definite upright component. In other respects this lead was normal. Thirteen cases (shown in Table I) had no significant electrocardiographic abnormality in the limb leads: None of these thirteen had T-waves in either Lead I or Lead II which were less than 2 mm. in amplitude, and none showed left axis deviation of more than 10 degrees, according to the formula of Carter, Richter, and Greene.<sup>2</sup> Case 10 had a  $Q_s$  wave but was included in this group because the heart was transverse in position.<sup>3, 4</sup> In the thirteen other cases (shown in Table II) the limb leads deviated from rigid normal standards, but the abnormalities were such that they could not be regarded as definite evidence of heart disease.

In all cases the chest lead was taken with the right arm electrode over the apex of the heart and the left arm electrode at the angle of the left scapula.  $T_1$  was upright in 20 and diphasic with a definite upright component in 6. An additional chest lead from the apex to the left leg was taken in 22 of the 26 cases; in one (Case 3, Table I) the T-wave of this

\*From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

TABLE I

CASE NO.	AGE	LIMB LEADS	T-WAVE IN CHEST LEAD	X-RAY OF HEART AND GREAT VESSELS	TYPE OF DISEASE
1	39	Normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
2	50	Normal	Upright	Normal	Angina pectoris
3	50	Normal	Upright*	Normal	Angina pectoris
4	45	Normal	Upright	Normal; substernal thyroid	Angina pectoris
5	21	Normal	Upright	Heart moderately enlarged; aortic configuration	Rheumatic heart disease with aortic insufficiency
6	34	Normal	Diphasic	Heart slightly enlarged	Old coronary occlusion
7	47	Normal	Upright		Angina pectoris
8	58	Normal	Upright	Heart slightly smaller than average	Angina pectoris
9	55	Normal	Upright	Normal	Angina pectoris
10	55	Q <sub>a</sub> wave	Upright	Heart normal in size; trans- versely placed	Angina pectoris
11	46	Left axis deviation $\angle -9$ degrees; otherwise normal	Upright	Normal	Old coronary occlusion
12	50	Left axis deviation $\angle -8$ degrees; otherwise normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
13	70	Left axis deviation $\angle -10$ degrees; otherwise normal	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris

\*In lead from apex to left leg T-wave was inverted.



TABLE II

CASE No.	AGE	LIMB LEAD ABNORMALITIES	T-WAVE IN CHEST LEAD	X-RAY OF HEART AND GREAT VESSELS	TYPE OF HEART DISEASES
1	47	T <sub>1</sub> 1 mm. high	Upright		Angina pectoris
2	51	T <sub>1</sub> 1 mm. high QRS complexes 5 mm. in amplitude	Upright	Heart slightly enlarged	Old coronary occlusion
3	47	T <sub>1</sub> 1 mm. high Q <sub>3</sub> wave	Upright	Normal	Angina pectoris
4	54	T <sub>1</sub> 1.5 mm. high	Upright	Heart moderately enlarged	Angina pectoris
5	60	Slight slurring of QRS complexes	Diphasic	Heart moderately enlarged	Old coronary occlusion
6	52	Low T <sub>2</sub> Inverted T <sub>1</sub> Q <sub>3</sub> wave	Upright	Heart moderately enlarged	Angina pectoris
7	66	Low T <sub>2</sub> Inverted T <sub>3</sub>	Upright		Paroxysmal cardiac dyspnea
8	54	T <sub>1</sub> 0.5 mm. high	Upright	Normal	Angina pectoris
9	45	T <sub>1</sub> 1 mm. high	Upright	Heart slightly enlarged	Angina pectoris
10	62	R <sub>1</sub> and R <sub>2</sub> = 5 mm.	Diphasic	Heart normal in size; aorta dilated and dense	Angina pectoris
11	52	Left axis deviation $\angle$ -31 degrees; otherwise normal	Upright	Heart slightly enlarged	Angina pectoris
12	51	Left axis deviation $\angle$ -42 degrees; otherwise normal	Upright	Heart normal in size; aorta dilated and dense	Angina pectoris
13	26	Right axis deviation $\angle$ +128 degrees; otherwise normal	Upright	Heart moderately enlarged; pulmonary artery prominent	Congenital heart disease

lead was inverted while  $T_4$  was upright; in the other cases the T-waves were similar in both these leads.

Roentgen ray study of the heart and aorta (film or orthodiagram) was carried out in 23 of the 26 cases (see Tables I and II). The heart was not enlarged in 14 cases; it was enlarged slightly in 4 and moderately in 5. The aorta was dilated and dense in 5 of the 14 patients who had no cardiac enlargement. Thus 9 of the 26 patients had no significant abnormality in either the roentgen ray examination or the electrocardiogram except the upright T-wave in Lead IV.

An examination of Tables I and II suggests that almost all adult cases showing an abnormal  $T_4$  as the only significant finding, have angina pectoris, or a history of coronary occlusion. However, our data should not be regarded as conclusive evidence upon this point: almost all cases of coronary occlusion or angina pectoris which come to our clinic are studied with chest leads, whereas cases not suspected of having coronary artery disease are not always examined in this way.

The following control groups were studied to determine in them the frequency of an upright  $T_4$ :

A. Eighty-one children: Forty-eight had rheumatic heart disease; 33 had no evidence of heart disease. Upright T-waves were found in Lead IV in approximately 25 per cent of each group. Our observations<sup>6</sup> are in line with those of other observers,<sup>7</sup> namely, upright T-waves in Lead IV may occur in children who have no evidence of heart disease.

B. Two hundred ninety-nine college students between the ages of sixteen and twenty-six years were examined with history, physical examination, orthodiagram, and electrocardiogram, with chest and limb leads. Only one showed an upright  $T_4$ . This patient had aortic insufficiency (Table I, Case 5). Three others had T-waves in Lead IV which were not strictly normal. The first had a blood pressure of 150/95, a heart rate of 110 per minute, and ventricular extrasystoles.  $T_1$  was isoelectric;  $T_2$  was slightly inverted;  $T_3$  was definitely inverted; and  $T_4$  was variable changing from plus 1 mm. to minus 1 mm. His tracing was repeated a few days later at which time  $T_1$  and  $T_2$  were plus 1 mm.;  $T_3$  was diphasic; and  $T_4$  was minus 1 mm. The second individual showed slight slurring of QRS;  $T_1$  was plus 1 mm.;  $T_4$  was diphasic, minus 2 mm. and plus 1 mm. After his electrocardiogram had been taken, he told us he had just run eight blocks to get to the appointment on time. Four days later, the tracing was repeated. The limb leads were much the same;  $T_4$  had become normal (-3 mm.). The heart rate was 120 per minute in both the tracings. The third was an athlete with a small heart.  $T_1$  was plus 1 mm.;  $T_2$  showed a peculiar contour with a slight terminal inversion;  $T_3$  was a "cove plane" wave, minus 1 mm.;  $T_4$  was diphasic, minus 2 mm. and plus 1 mm. All the rest of the 299 college students showed a definitely inverted T-wave in Lead IV. In 2 it was minus 1 mm.; in 1 it was minus 2 mm.; in the rest it was

minus 3 mm. or more. These statements apply only to the chest lead taken with the anterior electrode placed to the left of the sternum, and below the third left interspace. When the electrode was placed over the base of the heart, or near the right border, upright T-waves were sometimes found.

C. Forty-five women between the ages of sixty-two and eighty-five years were studied in a home for old women, through the kindness and with the assistance of Dr. John H. Arnett. This group cannot be considered a strictly normal one since, among other things, the blood pressure figures exceeded 170 systolic or 100 diastolic in thirty-eight cases. One individual showed a nearly isoelectric  $T_4$  and T-waves of low voltage in limb leads, not associated with other definite evidence of heart disease.\* Ten cases showed a T-wave in Lead IV with an upright component. In nine of these, the limb leads were definitely abnormal. In the tenth,  $T_1$  was low;  $T_2$  was isoelectric;  $T_3$  was inverted, and the patient suffered from cardiac complaints. These observations, though somewhat limited, suggest that there seems to be no tendency for  $T_4$  to become upright with age, except in the presence of other evidences of heart disease.

#### DISCUSSION

The significance of an upright T-wave in Lead IV has been discussed by Levine and Levine.<sup>8</sup> They found  $T_4$  upright in two patients who came to necropsy and showed no evidence of cardiac infarction. They write: "It is obvious, therefore, that an upright T-wave in Lead IV is of no value in the diagnosis of myocardial infarction. In fact, we have seen a positive  $T_4$  occur as a transient phenomenon during bronchopneumonia, as have others, and as a permanent or transient finding under a variety of other circumstances, such as mitral stenosis, uremia and hyperthyroidism." They also found an upright  $T_4$  in 9 of 100 cases of angina pectoris, in 7 of which "the customary three leads were normal." Their conclusion states that "upright T-waves in Lead IV were found when no infarction was present, and in fact where there was no significant heart disease."

Our opinion concerning the significance to be attached to an upright T-wave in Lead IV has been based upon an evaluation of the following observations: 1. The T-wave is notoriously unstable and is affected by a variety of factors. Digitalis, thyroid disease,<sup>9</sup> and intoxications of various types will cause it to change its direction. Exercise will cause significant T-wave inversion in limb leads in certain individuals, without evidence of heart disease.<sup>2</sup> In fact, there are certain persons, otherwise apparently normal, who have T-wave inversion in Lead II more or less

\*In three other cases the T-wave was normal in Lead IV, but was isoelectric in a lead taken with the right arm electrode at the apex, and the left arm electrode on the left leg.

constantly. Thus one should expect to find an occasional subject without demonstrable heart disease, whose T-wave in Lead IV is upright. 2. A T-wave in Lead IV which was isoelectric, or diphasic with a small upright component, was seen in certain cases in Groups B and C, when the limb leads were abnormal, but where signs of heart disease were not absolutely definite. 3. A certain proportion of presumably normal children show an upright  $T_4$ . 4. Only one of 299 college students had an upright  $T_4$  with normal limb leads. He was found to have rheumatic aortic insufficiency. 5. An upright  $T_4$  was found in ten of forty-five women over sixty years of age. All ten had other evidences of heart disease. 6. The cases reported in this paper, in which an upright  $T_4$  was the only definitely significant abnormality, showed, to say the least, a high incidence of serious heart disease. 7. We have not as yet seen an upright  $T_4$  in an adult in whom we were at all confident that "there was no significant heart disease," unless the patient had received digitalis.

We feel that the following comments should be made concerning the statements of Levine and Levine<sup>8</sup>: In the first place, an upright  $T_4$  occurs frequently in the absence of cardiac infarction. When present as an isolated finding, it is not a trustworthy sign of this lesion. However, in certain cases, it helps considerably to support this diagnosis, when changes in QRS are suggestive. Consequently, we disagree with the conclusion that it "is of no value in the diagnosis of myocardial infarction." In the second place, these authors make the statement that "upright T-waves in Lead IV were found . . . where there was no significant heart disease." In support of this statement, they refer to two patients, one who died of uremia, and the other who died of exsanguination from a bleeding peptic ulcer. They do not state the time interval between the taking of the tracing and the death of either patient. The electrocardiogram of the first patient shows an inversion of  $T_1$  and  $T_2$  (*Fig. 2F*).<sup>8</sup> The tracing of the second patient is stated to have shown an inversion of  $T_1$ ,  $T_2$ , and  $T_3$  (*Table III*).<sup>8</sup> No histologic studies of the heart muscle are presented. Now it is well known that definite poisoning of the heart muscle often occurs in uremia and that profound physiological changes may be produced in the myocardium by exsanguination. Moreover, T-wave inversions like those described in the limb leads of these two cases have been reported in very ill, and in moribund patients, presumably caused by pathological abnormalities of the heart muscle. Consequently, we interpret the statement of Levine and Levine<sup>8</sup> to mean that there was no primary, gross lesion of the heart in these cases, because they have not published evidence to establish the absence of considerable abnormality of the heart muscle. We stress this point since the simple statement that upright T-waves in lead IV were found where there was "no significant heart disease" might lead the reader to conclude that an upright  $T_4$  is not dependable evidence of myocardial abnormality. As a matter of fact, our observations indicate that an

upright  $T_4$  in an adult, obtained with the right arm electrode over the apex, is highly dependable evidence of such abnormality. Subsequent observation may bring to light an occasional case in which this sign is present when there is "no significant heart disease." However, no such case is known to us at present, in which digitalis has not been the probable cause of the T-wave change.

#### SUMMARY AND CONCLUSIONS

1. A group of 26 adult cases has been studied in which the only significant electrocardiographic abnormality was an upright T-wave in Lead IV or a diphasic  $T_4$  with a definitely upright component. In 13 of these cases, the limb leads conformed to rigid normal standards; in the other 13, the limb leads showed slight deviations from normal, but nothing that could be interpreted as definite evidence of heart disease.

2. The cardiac diagnoses made in these cases were as follows: in 17, angina pectoris; in 2, questionable angina pectoris; in 4, old coronary occlusion; in 1, paroxysmal cardiac dyspnea; in 1, rheumatic heart disease; and in 1, congenital heart disease.

3. The frequency of angina pectoris and coronary occlusion and the infrequency of other types of heart disease may be due in part to the types of material studied, since chest leads were made more often when coronary disease was suspected.

4. In the absence of digitalis medication, we have not seen an upright  $T_4$  in the electrocardiogram of any normal adult, when the anterior electrode was placed at the apex. Moreover, in our experience thus far, all adults with an upright  $T_4$  have given us reason to suspect the presence of heart disease.

5. A T-wave in Lead IV which was isoelectric, or diphasic, with an upright component of 1 mm. or less, has been seen in patients with abnormal limb lead electrocardiograms in whom the presence of definite heart disease could not be proved.

6. Our observations suggest that, when an adult has an electrocardiogram which is normal in every respect, except for a definitely upright element in the T-wave in Lead IV, this should be considered an important finding, and the patient should be studied carefully for other evidence of heart disease, especially coronary disease. It is unsafe to disregard this sign.

#### REFERENCES

1. Wolfarth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
2. Carter, E. P., Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Johns Hopkins Hosp. Bull.* 30: 162, 1919.
3. Pardee, H. E. B.: The Significance of an Electrocardiogram With a Large Q in Lead III, *Arch. Int. Med.* 46: 470, 1930.

4. Edeiken, J., and Wolferth, C. C.: The Incidence and Significance of the Deep Q-Wave in Lead III of the Electrocardiogram, *AM. HEART J.* 7: 695, 1932.
5. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion, *Bull. Am. Heart A.* 4: No. 5, 1935.
6. Rosenblum, H., and Sampson, J. J.: Study Lead IV of Electrocardiogram in Children With Special Reference to Direction of Excursion of T-Wave, *AM. HEART J.* 11: 49, 1936.
7. Lundy, C. J., McLellan, L. L., Bacon, C. M., and Merchant, R.: The Clinical Value of the Fourth Lead as Observed in 3,000 Ambulatory Patients. Presented before the American Heart Association, Atlantic City, June 11, 1935.
8. Levine, H. D., and Levine, S. A.: Electrocardiographic Study of Lead IV With Special Reference to Findings in Angina Pectoris, *Am. J. M. Sc.* 191: 98, 1936.
9. Rose, E., Wood, F. C., and Margolies, A.: The Heart in Thyroid Disease: II. The Effect of Thyroidectomy on the Electrocardiogram, *J. Clin. Investigation* 14: 483, 1935.

# ISCHEMIC PAIN IN EXERCISING MUSCLES\*

## ITS NATURE AND IMPLICATIONS

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### INTRODUCTION

WHILE the phenomenon of ischemic muscular pain lends itself readily to experimental observation by the use of a relatively simple technic, the number of metabolic factors which conceivably influence its behavior are numerous and are separable with difficulty so that the effect of each may be critically evaluated. From the possible methods of approach to this problem which might be adopted, we have selected those which aim to evaluate the rôle that the production and disposal of lactic acid may play.

The mere fact that pain occurs in exercising muscle deprived of blood has been known for many years, but it is only recently that this phenomenon has been subjected to careful experimental observation. The investigations of Sir Thomas Lewis and his associates<sup>1</sup> on this subject, which have in the main been corroborated by other observers, have laid the groundwork for our present conceptions which may profitably be summarized as follows:

1. Production of the pain substance is intimately concerned with the normal metabolic changes occurring during and after contraction of a skeletal muscle.

2. The pain substance is produced by a contracting muscle the circulation of which is free, but obstruction of the arterial flow, or decrease in the oxygen-carrying power of the blood, materially increases its speed of accumulation.

3. Under experimental conditions the phenomenon of muscular fatigue may be easily divorced from the occurrence of pain.

4. The pain substance is diffusible and under normal circumstances is rapidly washed away or destroyed. When the circulation is impeded, the substance which escapes from the muscle fiber may reach a concentration in the tissue spaces sufficient to stimulate sensory nerve endings. When circulation is reestablished, it is at once washed away and pain consequently ceases, but this does not necessarily mean that the metabolism of the muscle fiber has returned to normal.

The above facts seem well established. Further observations<sup>2-6</sup> suggest that:

1. Of the factors which are operative in dissipating the pain upon return of the circulation to an ischemic limb, the bringing of oxygen is

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of importance as well as is the mechanical dilution or washing out. If the oxygen content of the intrushing blood is materially decreased, the pain persists or dies out slowly.

2. The oxygen content of the blood is also of importance in determining the rate of formation of the pain substance in that, if it be sufficiently lowered, concentration of pain substance may rise to the point of stimulating sensory nerve endings even if the circulation to the limb remain unimpeded.

3. Certain observations suggest that the substance may be produced, although extremely slowly, in resting muscles deprived of blood. The evidence here is indirect and requires cautious interpretation.

4. Recent studies<sup>7</sup> have been offered as demonstrating that the pain substance can be trapped in resting muscles distant from its point of origin, but here again the evidence is not beyond criticism.

Insight into the chemical nature of the pain substance and its relation to the metabolic processes governing the expenditure of energy in the form of muscular contraction and recovery has up to now been entirely a matter for conjecture. It has been repeatedly suggested that the substance is probably an acid metabolite, and it is not surprising that lactic acid, known to be produced by contracting muscle and to be easily diffusible from it, has been suggested as the culprit. No studies aiming to establish definitely or to disprove such an hypothesis have to our knowledge as yet been undertaken.

Before presenting our observations it might be well to summarize the present knowledge<sup>8</sup> regarding the formation and fate of lactic acid in the body and to see if the laws governing lactic acid metabolism, in relation to muscular contraction, may be found consonant with or contrary to the known behavior of the pain substance. We do not here wish to enter into a discussion of muscular metabolism except so far as it bears upon the problem at hand. Lactic acid is derived from the breakdown of muscle glycogen. The rôle of this reaction in the immediate liberation of energy for muscular contraction is probably not important, but at the same time the reaction itself is an obligatory one. Under conditions of rest lactic acid production proceeds so slowly as not to exceed its rate of disposal, but upon muscular contraction its formation is at once increased many fold, and, if such contraction be repeated rapidly, the rate of formation quickly exceeds the possibilities for disposal within the muscle itself and lactate ion diffuses into the tissue spaces, to be picked up in some measure by the circulating blood. At a given moment, then, the concentration of lactic acid in the muscle will depend upon the ratio of rate of production to rate of disposal, and the concentration in the tissue spaces and blood will in addition be influenced by the rapidity of diffusion from the muscle cell and the adequacy of the circulation as determining its mechanical removal. Thus in severe sustained exercise the lactic acid content of



the blood is materially increased and may remain at a higher than normal level for an hour or longer. It is believed that in such circumstances lactate ion diffuses with facility both into the liver, where it is rebuilt into glycogen and, what is of great importance as regards the problem at hand, into resting muscles which have not participated in the preceding exercise.<sup>9</sup> Of the total amount of lactic acid formed during exercise, approximately one-fifth is later burned to carbon dioxide and water; the remainder, except for the escape of a small quantity through the kidneys, is reconverted into glycogen, primarily by the liver. These reactions occur during the recovery period following exercise. It should be emphasized that oxygen must be available before these changes can be accomplished. In contradistinction to the anaerobic release of energy making muscular contraction possible, the recovery phase is strictly contingent upon the presence of oxygen. It follows from this that any circumstance interfering either with the oxygen-carrying capacity of the blood or with sufficient irrigation by normal blood will lead to a local or general piling up of lactic acid in the tissues bearing the brunt of such disturbance.

To summarize: Lactic acid is rapidly produced by contracting muscle; it diffuses readily into the tissue spaces and blood stream; a large portion of it may be washed away from its point of origin if the circulation is adequate; its ultimate disposal by burning and by reversion to glycogen demands available oxygen; if the blood concentration is sufficiently high, it may readily diffuse into resting muscles. Certain similarities between this behavior and that of the pain substance are at once apparent. The formation of both is an accumulative process when occurring during repeated muscular contraction. The concentration of each rises rapidly when circulation is impeded or when available oxygen is not present. Both diffuse readily from the muscle fiber into the tissue spaces. Available knowledge regarding the behavior of the pain substance does not allow us to draw this analogy further, but it may be said that to this point mutually exclusive characteristics of behavior are not encountered.

It is the purpose of this paper to present detailed observations which aim to test the hypothesis that lactic acid and the pain substance are identical. While a final answer cannot be given on the basis of our observations, it will be shown that this hypothesis adequately explains the experimental results obtained and that at least production and disposal of both lactic acid and pain substance are subject to similar metabolic laws.

#### METHODS

Our observations were conducted upon a group of four healthy young adults using a technic similar to that resorted to by other observers. With the blood supply occluded by a pressure of 200 mm. of mercury thrown upon the upper arm, a weight of 1,600 gm. was pulled through

a distance of 6.0 cm. by a submaximal grasp of the fingers at a rate of once a second. The time of onset of the pain, although found so variable as to prove of little ultimate significance, was noted in each instance, but the observation was terminated at the point where pain of the forearm became so severe as to preclude further muscular contraction. This end-point was found to be quite sharp in every instance and only rarely was it necessary to cease the determination because of fatigue, which was only encountered when the usual exercise tolerance was greatly exceeded. A gradual gain in ischemic exercise tolerance, which occurred over a period of months, is illustrated by Chart 1. The tolerance of the left arm was appreciably less than that of the right (all right-handed).

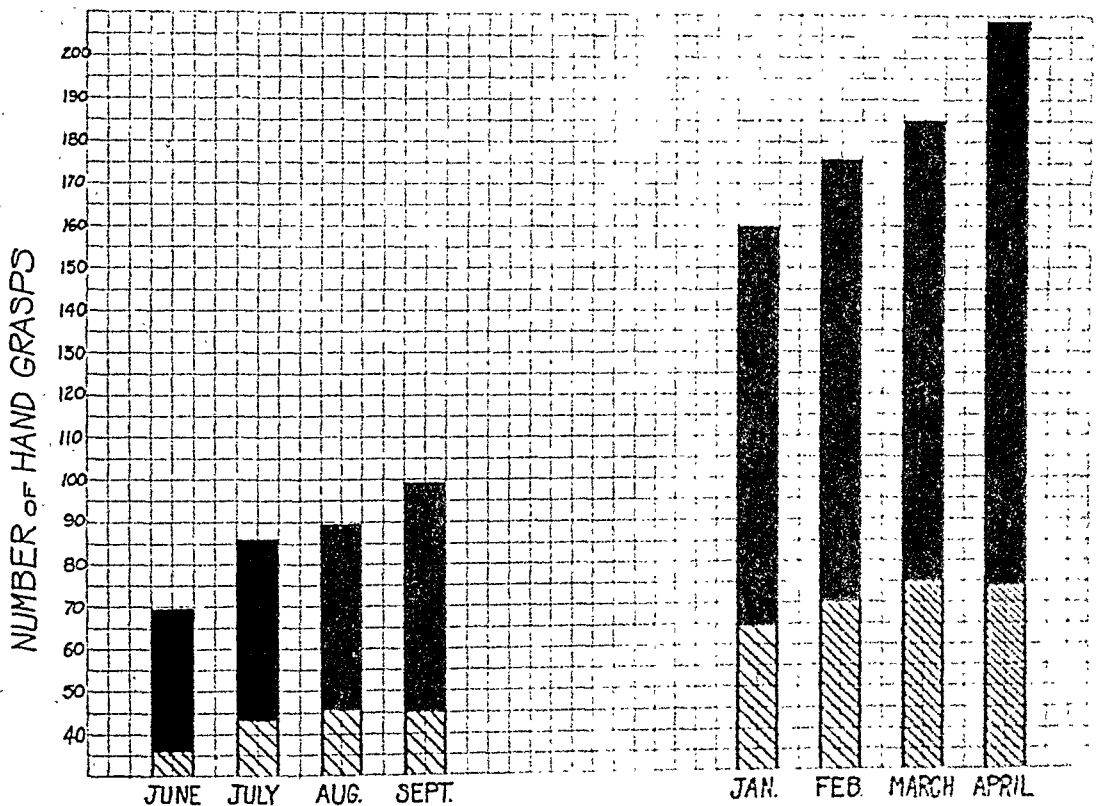


Chart 1.—Increase in forearm exercise tolerance over a period of months.

The level of lactic acid in the blood was determined on oxalated specimens taken from the veins of the resting forearm without stasis. The method of Mendel and Goldscheider was used. The percentage of error in our laboratory is approximately  $\pm 10.0$ . Blood sugar was determined on venous blood by the method of Schafer and Hartmann.

#### RESULTS

As the first step it became necessary to establish control levels for the ischemic exercise tolerance of each individual. It was found that the exercise tolerance of one arm could be determined immediately following that of the other without its being appreciably influenced by this sequence. By studying the influence of varying the time intervals

between successive determinations conducted on the same arm, it was demonstrated that a rest period of fifteen minutes was sufficient to insure complete recovery of the exercised muscles. It was thus possible to measure the exercise tolerance of the same arm at fifteen-minute intervals over a period of two hours without exceeding a maximum variation of 15 contractions (7 per cent) above or below the value for the first determination and, in most observations, this variation was not greater than 5. As a further means of checking the possible influence of fatigue upon the frequently exercised muscles of one arm, the tolerance of the other arm was measured initially, after one hour, and at the conclusion of the second hour. These values were likewise found to vary little from one another. In most instances it was impossible to continue the observations longer than two hours because fatigue prohibited continuance of the exercise to the point of intolerable pain. However, this period of time proved sufficient for the purpose of these studies.

The consistency in behavior of the exercised forearm under conditions of bodily rest being thus established, the first problem investigated was that of the effect of nonischemic exercise of the leg muscles upon the pain tolerance of the forearm. The subject exercised upon a stationary bicycle peddling against a load as rapidly as possible until stopped by exhaustion. The arms were kept strictly at rest during this period, grasping of the handlebars being avoided. At the conclusion of the exercise the subject was seated in a chair and the exercise tolerance of the right forearm, checked at intervals by that of the left, was observed over a period of two hours in a manner identical with the control procedure. Occasionally an increase in the number of contractions possible was observed immediately at the close of the exercise period but an abrupt fall in tolerance occurred after an interval of fifteen minutes. In the succeeding determinations, intolerable pain developed at a progressively lower number of contractions until the thirtieth or forty-fifth minute, after which there was a gradual return of the forearm exercise tolerance toward the initial level which was usually reached in from 75 to 105 minutes. In Chart 2 the results of such an experiment are indicated in terms of number of contractions below the control level. The shape of this curve, which is characteristic of that encountered in numerous experiments of this kind, is strikingly different from the control curve also charted. It was further found that the decrease in exercise tolerance of the forearm resulting from exercise of the legs was roughly proportional to the intensity and duration of the latter. These results could be attributed either to changes in circulation through the resting forearm consequent upon acceleration of the circulation from leg exercise, or to an escape into the blood of a substance or substances formed in the exercising leg muscles which then diffused into the tissues of the forearm in sufficient quantity to augment the effect of the pain

substance produced by the ischemic forearm muscles themselves. The first hypothesis is unlikely because the effects observed persisted for some time after the pulse acceleration consequent upon the leg exercise had subsided.

The blood lactic acid values determined upon blood taken from the unexercised forearm at fifteen-minute intervals throughout the course of the experiment are likewise expressed on the chart. The curve is similar to those published by Hill, Long, and Lupton.<sup>8</sup> There is a precipitous rise immediately after the exercise, followed by a slow downward slope until the initial level is reached at the ninetieth minute. The similarity in shape between this curve and that of the exercise tolerance of the forearm is striking.

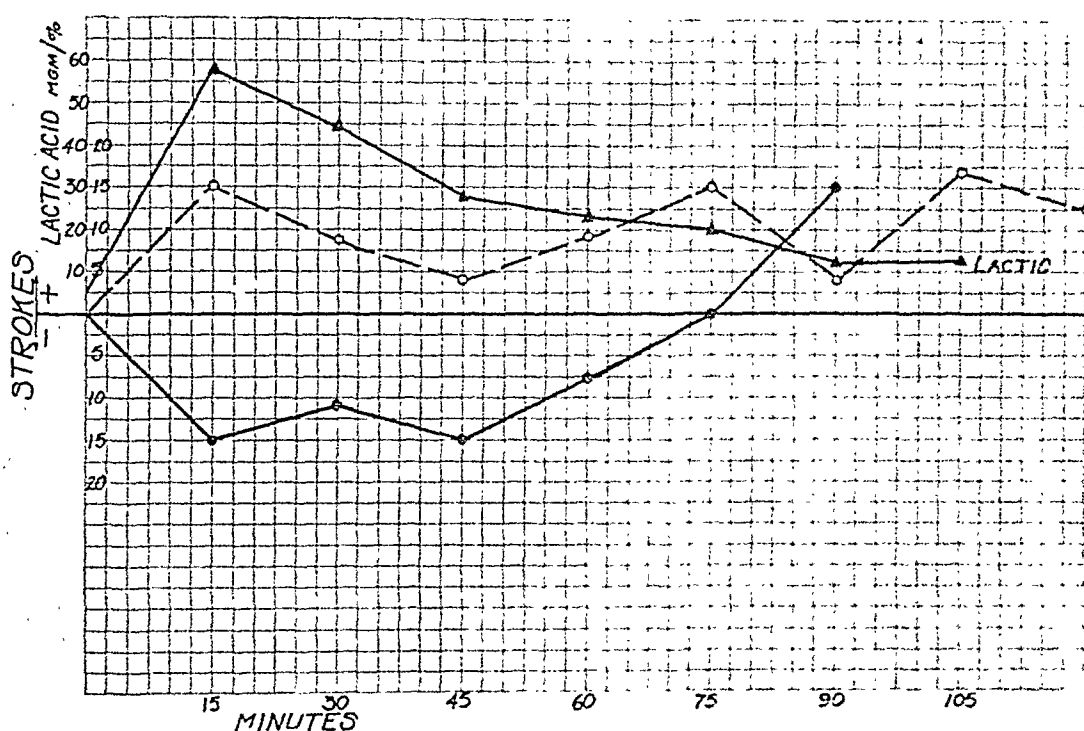


Chart 2.—Effect of vigorous leg exercise upon forearm exercise tolerance.

The next question to be studied was: Is the substance which escapes from exercising muscles with free circulation similar to, or identical with, the pain substance produced during ischemic exercise? As an approach to this problem, after numerous trials, the following experimental procedure was adopted: After determining the exercise tolerance of both forearms during bodily rest, the subject lay supine upon a bed with the legs elevated by two pillows. The circulation of each leg was then occluded above the knee, and the feet were forcefully extended and flexed once a second to the point of intolerable pain when the circulation was immediately reestablished. This procedure was repeated from three to six times with intervening rest periods of three minutes. The number of flexor-extensor movements of the feet possible under these conditions was found to decrease with each bout of exercise.

falling from an initial level of 70 to 80 movements to from 40 to 60. Parenthetically, it might be observed that an exercising nonischemic leg, under these conditions, will likewise become painful after a minute or two but that the exercise can be continued to the point of fatigue, pain increasing but slowly.

At the conclusion of the foot exercises the subject was seated in a chair. The exercise tolerance of the forearms was determined in a manner identical with that of the preceding experiment. A sample protocol is illustrated by Chart 3. The results were consistent and striking in all experiments. Here again a progressive loss in tolerance occurred which was far in excess of the variations encountered during the control determinations and which persisted over a period of from

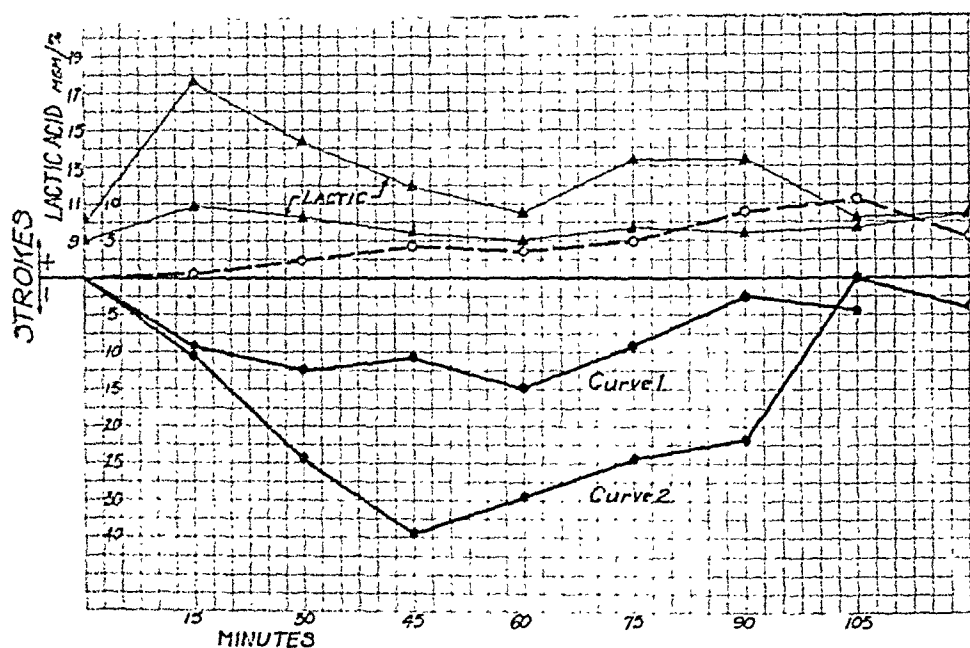


Chart 3.—Effect of release of pain substance from the legs upon the forearm exercise tolerance. Curve 1, after 3 releases. Curve 2, after 6 releases.

90 to 120 minutes. As illustrated by curves 1 and 2 (Chart 3), it was further found that the effect upon the muscles of the forearm was influenced by the number of times that the pain was built up in the legs. The lower curve shows the effect from six exercise cycles; the upper, that from three. These experiments demonstrate conclusively that pain substance built up in one group of ischemic exercising muscles escapes into the blood stream and circulates there for an appreciable length of time, which allows of its being trapped in other portions of the body where the effect of its presence may be unmistakably recognized. Is this effect traceable to an increase in the concentration of lactic acid in the blood? Lactic acid determinations conducted throughout the course of such experiments have shown a small but quite consistent elevation of the level in venous blood. Direct sampling of arterial

blood, which would allow a more satisfactory estimate of the concentration of lactic acid being brought to the forearm muscles, was not practical, but in one experiment samples of blood were taken from a forearm which was constantly immersed in warm water. The concentration in these samples, which should approximate closely the concentration present in the arterial blood itself, was slightly higher than in those of venous blood taken from the cool forearm.

It will be noted that the concentration of venous lactic acid returns to the initial level some minutes before the forearm exercise tolerance has reached the control value. The significance of this observation will be commented upon later.

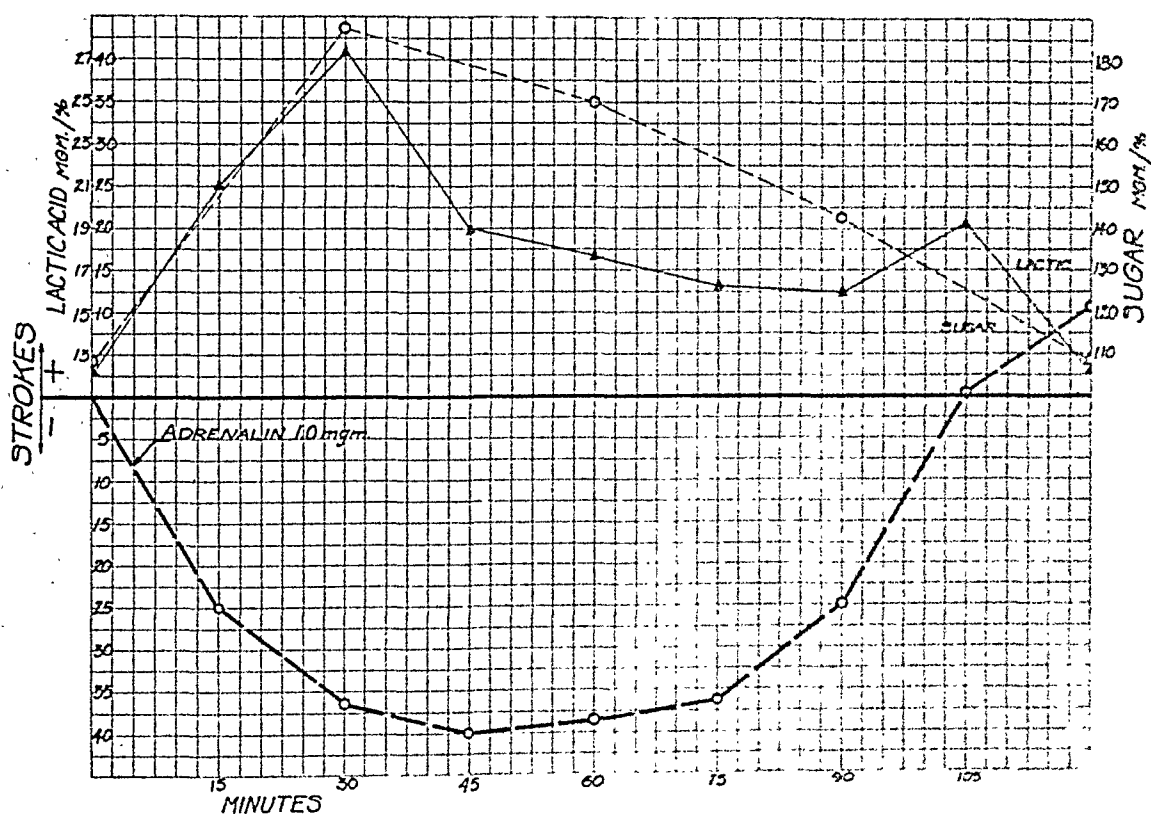


Chart 4.—Effect of 1 mg. of adrenalin upon forearm exercise tolerance.

The next group of observations was concerned with a study of the effect of increased blood lactic acid concentration, brought about by other means than exercise, upon the exercised forearm. In Chart 4 the effect of the intramuscular injection of 1.0 mg. of epinephrine upon the levels of sugar and lactic acid in venous blood, as correlated with the forearm exercise tolerance, is illustrated. It will be recalled<sup>10, 11</sup> that adrenalin exerts a profound influence upon the carbohydrate metabolism of muscle. Its primary effects are to accelerate the breakdown of muscle glycogen into lactic acid and probably to inhibit the utilization of sugar brought to the muscle. In the blood these influences are reflected by lactic acidemia and, in part, by hyperglycemia. As Chart 4 shows, the effect persists for about two hours, and the curve for decrease in forearm exercise tolerance was, in our experiments, of the same pattern as,

but in opposite direction to, those illustrating the concomitant changes in the blood. Since, however, lactic acidemia from epinephrine is accompanied by hyperglycemia, it was necessary to determine the influence of the latter upon the exercised forearm muscles. We sought to determine if hyperglycemia influenced either the speed of formation of pain substance in the ischemic forearm muscles themselves, or the fate of the pain substance released from the legs. The fasting subject, immediately after the tolerance for ischemic exercise of each forearm had been ascertained, consumed 100 gm. of glucose. Changes in exercise tolerance of the forearm were then observed at fifteen-minute intervals in the usual manner. In several such experiments a surprising rise in the number of contractions possible was found during the latter part of the

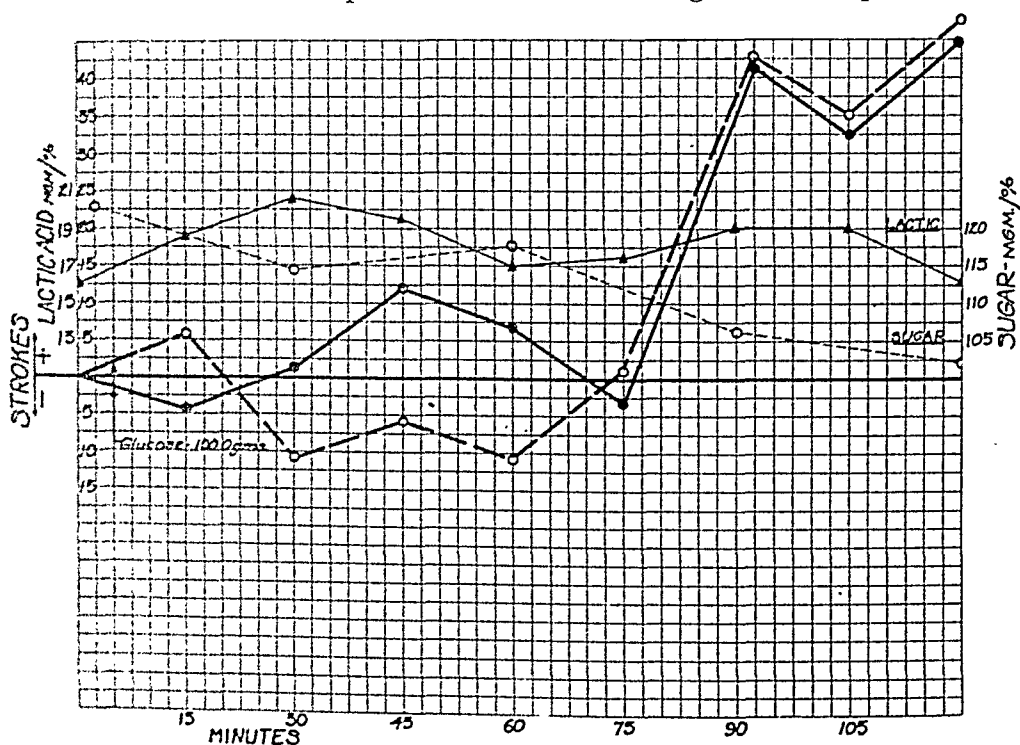


Chart 5.—Effect of 100 gm. of glucose upon forearm exercise tolerance with and without release of pain substance from the legs.

two-hour period, the subject often being forced to stop the exercise from fatigue rather than from pain. When a study of the concentration of the pain substance in the blood after its release from the legs was attempted, following glucose administration, an increased concentration could not be demonstrated by trapping in the forearm. The usual decrease in forearm tolerance was entirely lacking. The curve coincided closely with that obtained in the first or control glucose experiment. These results are illustrated in Chart 5, including the venous blood sugar values, which in this subject showed no rise. The curve for blood lactic acid during this experiment is similar to those obtained when glucose is not administered. Also, intolerable pain developed in the legs just as quickly. Evidently the effect of glucose upon the rapidity of production of pain substance is not apparent until approximately

75 or more minutes have elapsed from the time of its ingestion. The leg exercises were initiated immediately after the ingestion of the glucose, and during the first half hour (the time necessary to complete six cycles of leg exercise) no increase in tolerance of the forearms was noted in the control experiment.

That the presence of pain substance in the blood following release from the legs is no longer recognizable from its effect upon forearm exercise tolerance is difficult to explain. Either the metabolism of the muscles is significantly changed by glucose ingestion, or else, which is more unlikely, hyperglycemia in some manner inhibits diffusion of pain substance from blood to tissues. These results merit further investigation.

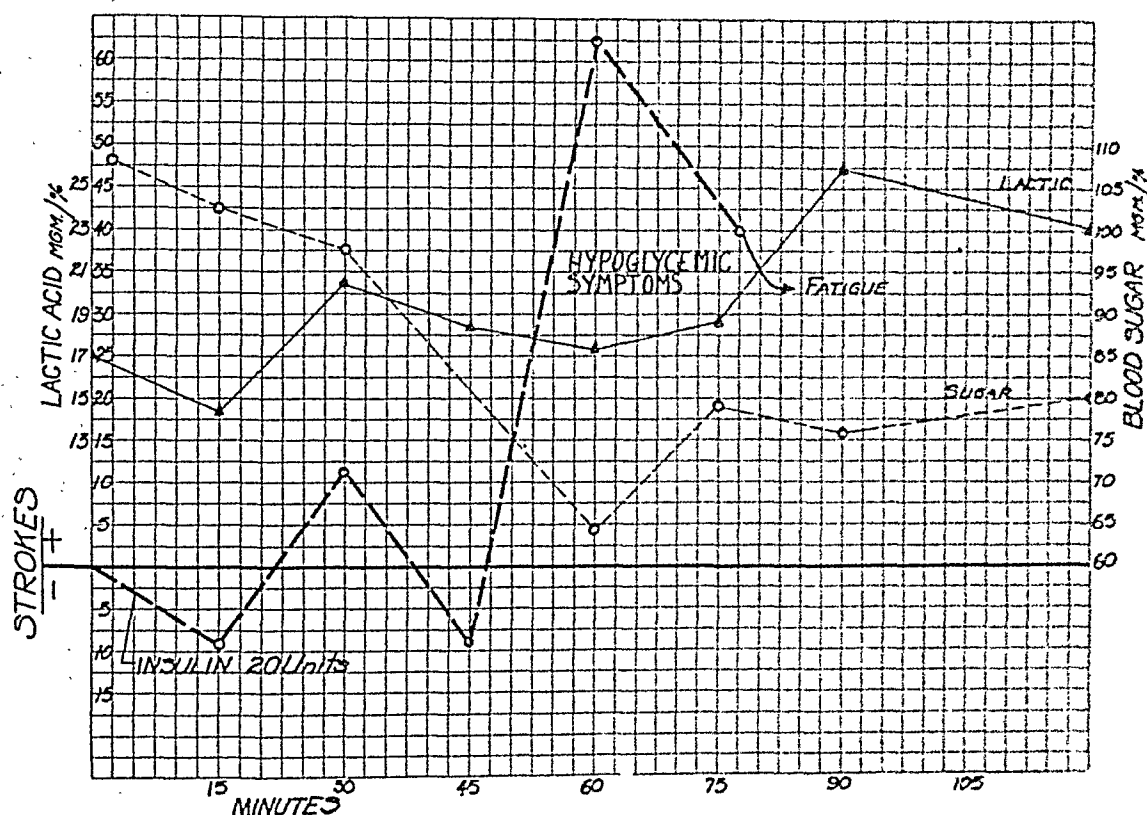


Chart 6.—Effect of hypoglycemia upon the forearm exercise tolerance.

The effect of hypoglycemia upon the formation and fate of the pain substance has been observed in a few instances. The experimental procedure was identical with that above except that the intramuscular administration of 20 units of insulin was substituted for ingestion of glucose. In two such experiments consistent effects upon forearm exercise tolerance, with or without release of pain substance from the legs, could not be demonstrated. However, the subject did not experience hypoglycemic symptoms. In a third experiment upon another subject the blood sugar fell from 106 to 64 mg. per cent within one hour. This fall was accompanied by rather pronounced symptoms, but exercise of the forearm could be continued well beyond the point at which intolerable pain became evident in the control determination. Blood lactic acid was not elevated during this time. Determination of exercise tol-



erance beyond the sixty-minute interval was not satisfactory because of muscular fatigue, but the onset of pain appeared to be delayed. At the conclusion of two hours following insulin, there was an appreciable lactic acidemia which might be the result of compensatory outpouring of adrenalin. This course of events (Chart 6), difficult of interpretation as regards specific effects upon the pain substance, should be corroborated by further study.

The last group of experiments is concerned with the effect upon ischemic pain of the administration of sodium lactate by the oral and intravenous routes. The sodium lactate for oral ingestion was prepared by adding sodium bicarbonate to a weighed amount of acid in sufficient quantity to bring the pH to approximately 6.0. The mixture was then

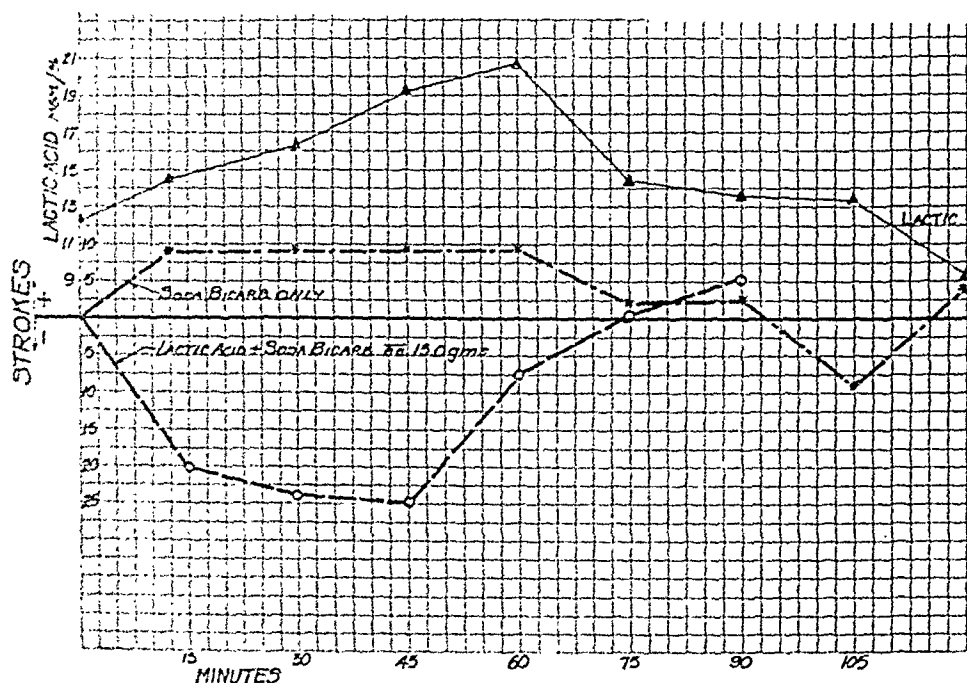


Chart 7.—Effect of the oral ingestion of lactic acid plus sodium bicarbonate and of sodium bicarbonate only upon forearm exercise tolerance.

diluted to a volume of 200 c.c. and taken when fasting. Forearm exercise tolerance was measured before and after this in the usual manner. The dosage of sodium lactate varied from 10 to 20 gm. In some experiments exercise tolerance was not influenced, and the subject had a bowel evacuation within a comparatively short period following its ingestion. In one such experiment it was found that the blood lactic level was not elevated, indicating lack of absorption from the intestinal tract. In another experiment there was an appreciable decrease in exercise tolerance, which persisted for over an hour, but no change in the level of venous lactic acid. In the remaining experiments, a sample of which is given in Chart 7, there was both a drop in the number of hand grasps possible and a concomitant lactic acidemia. In a control experiment following the ingestion of an amount of sodium

bicarbonate equal to that used for the neutralization of the lactic acid preparation, namely 15.0 gm., no effect upon the muscles of the forearm was evident.

In a final experiment, 60 c.c. of molar sodium lactate (approximate content 6.0 gm.) diluted to a volume of 180 c.c. was administered intravenously. As illustrated in Chart 8, concentration of blood lactic acid rose from 25 to 38 mg. per cent during the injection. At its conclusion the level had fallen to 32.9 mg. It continued to fall during the next thirty minutes until a low concentration of 20 mg. per cent was reached. The immediate decrease in forearm exercise tolerance during the injection was striking. The exercise curve continued downward, reaching its lowest point simultaneously with that of the blood lactic acid. After

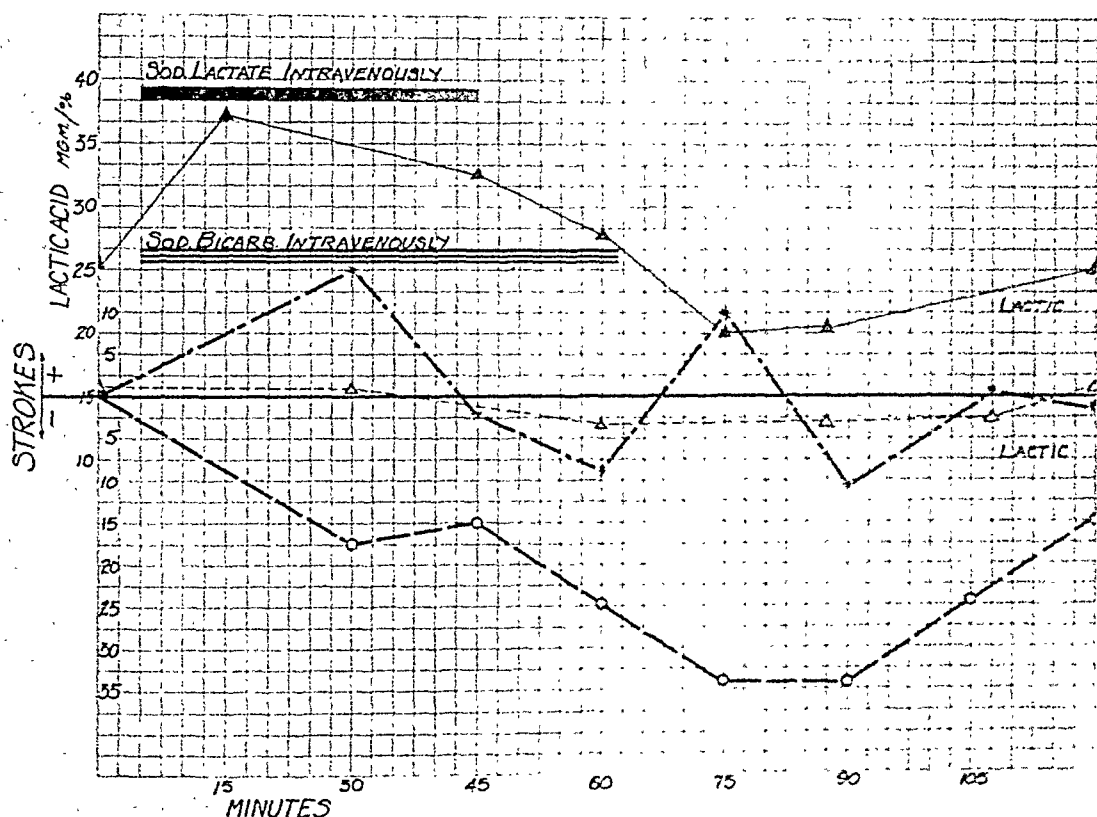


Chart 8.—Effect of the intravenous administration of sodium lactate (60 c.c. molar solution) and of sodium bicarbonate (6.0 gm.) upon forearm exercise tolerance.

this, it turned abruptly upward but did not reach the control level within two hours. At this time, the observations had to be terminated because of fatigue of the forearm, the pain end-point proving unattainable. It was likewise necessary to control this experiment by the giving of an equivalent amount of sodium bicarbonate in a solution of equal hypertonicity. That neither a significant change in exercise tolerance nor in blood lactic acid content resulted is shown in Chart 8.

#### DISCUSSION

Before attempting to analyse the observations herein reported as regards their bearing upon what we might term the lactic acid hypothesis, attention should be called to certain factors which might easily obscure their significance. In the first place, all blood analyses were done on

venous samples, which may not give a true picture of the potentiality for the diffusion of lactate ion from blood to muscle and tissue spaces. In other words, the level of lactate ion in blood returning from resting muscle may be normal, and yet its concentration in and about the muscle actually increased as the result of diffusion from arterial blood containing a higher than normal content. This might serve to explain in part the fact that in many experiments the exercise tolerance of the forearm did not return to the initial level until some minutes after the blood was found to be carrying a low content of lactic acid. It is possible that the concentration of lactate ion in the muscle may remain increased for an appreciable time after it is no longer augmented by diffusion from the arterial blood stream. Another fact of possible significance is that the concentration of lactate ion in the muscle would, under rest, reach an equilibrium with that of the plasma, which is 33 per cent greater than the concentration in whole blood.<sup>8</sup> Our observations were conducted at fifteen-minute intervals, and it would seem that if the blood lactic acid content were changing rapidly, the rest periods were hardly ample enough to insure that a state of equilibrium between blood and tissues had actually occurred at the time of the observation. Assuming, then, that lactic acid accumulation in and about sensory nerve endings is in fact immediately responsible for the occurrence of ischemic pain, it would appear from the above considerations that analyses of venous blood would at best reflect only indirectly the magnitude of such accumulation and therefore a strict parallelism between exercise tolerance and blood lactic acid content could hardly be expected in all experiments. An analysis of our observations from this point of view at once discloses some significant facts. Lactic acidemia, as brought about by exercise, epinephrine, or the introduction of sodium lactate into the body, was regularly accompanied by an earlier appearance of ischemic pain in the muscles of the forearm. In most experiments this effect outlasted the rise in blood lactic acid content, but in no instance did exercise tolerance return to normal in the face of continuing lactic acidemia. The converse of this was not always true, namely, decreased forearm exercise tolerance often occurred without rise in blood lactic acid but, for reasons previously stated, the inference must not necessarily be drawn that the concentration of lactate ion about the nerve endings was likewise low. We do not regard this evidence, therefore, as entirely unharmonious with the provisions of the hypothesis. It is further apparent that the degree of hastening of the pain end-point was not in proportion to the intensity of the lactic acidemia. The maximum decrease in the possible number of hand grasps observed in our experiments was 40 (21 per cent), and this occasionally occurred at a time when the concentration of lactic acid in the blood had returned to normal. This lack of parallelism between the two phenomena can be explained by assuming that the tissues of the forearm are capable of taking up only a maximum fixed amount of lactate ion by diffusion from arterial blood and that the speed of its

accumulation might vary with the content of lactic acid in the arterial blood coming in contact with them. During the initial stages of lactic acidemia, the rate of diffusion of lactate ion from blood to tissues should be rapid, but as the tissue concentration rises, the diffusion rate in this direction might proportionately decrease until the blood lactate level becomes low, at which time it is reasonable to suppose that the direction of diffusion reverses itself, lactate ion now passing from tissues to blood. This conception adequately explains the typical course of events seen in most of our experiments; namely, a rapid drop in exercise tolerance during the first fifteen or thirty minutes of induced lactic acidemia when the diffusion rate is rapid, a flattening out of the curve as diffusion from blood to tissue becomes slow, a gradual recovery by reversal of direction of diffusion occurring after the concentration in the blood has fallen to normal.

Some of our experimental observations, however, are not in strict agreement with the hypothesis that lactic acid is the sole substance responsible for ischemic muscular pain. In some of the experiments dealing with trapping of the pain substance in the forearm after its release from the legs, no rise in lactic acid content of the blood was encountered, whereas the decrease in forearm exercise tolerance was consistent and unmistakable. Likewise, its magnitude was quite comparable with that occurring from induced lactic acidemia. This may well indicate that another substance or substances may be capable of producing ischemic pain. In one such experiment the level of inorganic sulphate of the blood was followed, but no appreciable change occurred. Anrep and von Sallfeld<sup>12</sup> have recently shown that there is released from contracting muscle a stable vasodilator substance which they identify, on the basis of biologic assay, as histamine. We carefully sought for evidences in our experiments of histamine effect upon the general circulation following repeated release of pain substance from the legs. No fall in blood pressure or flushing was ever observed, nor was the electrocardiogram altered. In many subjects, however, a slight fall in pulse rate, varying from 6 to 10 beats, occurred in from eight to twelve minutes after the sixth release. This phenomenon is worthy of further study, particularly since a similar occurrence has recently been noted in cardiac patients following work on the ergometer.<sup>13</sup>

Another series of observations which are not strictly in accord with the lactic acid hypothesis are those dealing with the effect of glucose upon the formation and disposal of the pain substance. It will be recalled that the exercise tolerance of the forearm was materially increased and the trapping of pain substance could not be accomplished. In one such experiment there was a slight rise in the concentration of blood lactic acid, but no alteration of forearm exercise tolerance was demonstrated.

#### CONCLUSIONS

Our conclusions from the evidence herein presented are:

1. The substance or substances responsible for pain in exercising

ischemic muscles are relatively stable, may be present in the blood stream for an appreciable period following their release from such muscles, and may diffuse into tissues distant from their point of origin.

2. Such substance or substances are produced likewise in nonischemic exercising muscles, and their concentration in the blood stream following vigorous exercise is materially increased for an hour or longer.

3. Increase of lactate ion in the muscles of the forearm, brought about by whatever means, uniformly enhances the action of the pain substance produced by these same muscles.

4. Probably an increased concentration of lactate ion about the sensory nerve endings can, per se, produce pain, such increase not necessarily exceeding metabolic limits.

5. It is possible that lactate ion is solely responsible for the production of ischemic pain, but release of other substances, which are beyond doubt subject to similar metabolic laws, may play a rôle, and these should be investigated.

We wish to thank the volunteers who subjected themselves to these experiments and Miss L. Jemtgaard for technical assistance.

#### REFERENCES

1. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, *Heart* 15: 359, 1929-31.  
Lewis, T.: Pain in Muscular Ischemia: Its Relation to Anginal Pain, *Arch. Int. Med.* 49: 713, 1932.
2. Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, *J. Clin. Investigation* 13: 37, 1934.
3. Perlow, S., Markle, D., and Katz, L. N.: Factors Involved in the Production of Skeletal Muscle Pain, *Arch. Int. Med.* 53: 814, 1934.
4. Katz, L. N.: Mechanism of Pain Production in Angina Pectoris, *AM. HEART J.* 10: 322, 1935.
5. Laplace, L. B., and Crane, M. P.: Observations on the Production of Pain and Fatigue in Muscular Ischemia and Their Relationship in Angina Pectoris, *Am. J. M. Sc.* 187: 264, 1934.
6. Pickering, G. W., and Wayne, E.: Observations on Angina Pectoris and Intermittent Claudication in Anemia, *Clin. Sc.* 1: 305, 1934.
7. Katz, L. N., Lindner, E., and Landt, H.: On the Nature of the Substance (s) Producing Pain in Contracting Skeletal Muscle: Its Bearing Upon the Problems of Angina Pectoris and Intermittent Claudication, *J. Clin. Investigation* 14: 807, 1935.
8. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, 1931, Williams and Wilkins Co., Vol. 1, p. 474.
9. Hill, A. V., Long, C. H., and Lupton, H.: Muscular Exercise Lactic Acid, and the Supply and Utilization of Oxygen, *Proc. Roy. Soc., London, Series B.* 96: 438, 1921.
10. Meyerhof, O.: The Chemistry of Muscular Contraction, *Lancet* 219: 1415, 1930.
11. Hill, A. V.: The Revolution in Muscle Physiology, *Physiol. Rev.* 12: 56, 1932.
12. Editorial, *J. A. M. A.* 101: 1078, 1933.
13. Barr, D. P., Himwich, H. E., and Green, R. P.: Studies in the Physiology of Muscular Exercise, *J. Biol. Chem.* 55: 495, 1923.
14. Cori, Carl F.: Carbohydrate Metabolism, *Physiol. Rev.* 11: 143, 1931.
15. Hirschhoff, F., and Long, M. L.: Depletion of Muscle Sugar by Adrenalin, *Am. J. Physiol.* 95: 403, 1930.
16. Anrep, G. V., and von Sallfeld, E.: The Blood Flow Through the Skeletal Muscle in Relation to Its Contraction, *J. Physiol.* 85: 375, 1935.
17. Biering, E., Larsen, K., and Nielsen, E.: Some Cases of Slow Pulse Associated With Electrocardiographic Changes in Cardiac Patients After Maximal Work on the Krogh Ergometer, *AM. HEART J.* 11: 416, 1936.

## CREATINE CHANGES IN HEART MUSCLE UNDER VARIOUS CLINICAL CONDITIONS\*†

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THE establishment of a satisfactory explanation of the physiology of skeletal muscle contraction on a chemical basis involving phosphocreatine has revived interest in the chemistry of heart muscle under various clinical and experimental conditions. The new approach seems to offer some promise of elucidation of such intricate problems as the finite basis of myocardial weakness, of cardiac hypertrophy, and perhaps even of pharmacodynamic action. A more fundamental explanation of heart failure has long been demanded by clinicians, impressed by the frequent absence of adequate gross and microscopic findings to explain the clinically observed complete functional insufficiency of the cardiac musculature.<sup>1</sup> That something more than morphological changes must be sought out has been frequently indicated, and that biochemical changes may play an important rôle has been suggested.

### BIOCHEMICAL BACKGROUND

Constabel<sup>2</sup> in 1921, following the earlier suggestion of Pekelhering<sup>3</sup> that increased muscle tonus was associated with higher creatine content, found that the creatine content of atonic, dilated or damaged human hearts was usually low. These observations were apparently lost for thirteen years. During these intervening years, however, the great mass of experimental work on the physiological chemistry of skeletal muscle contraction has been carried out in Germany, in England, and in the United States. Since 1922 significant contributions to our knowledge of this subject of muscle physiology have been published from Embden's laboratory. In one of the early papers Embden and Lawaczek<sup>4</sup> presented observations of reactions which demonstrated the importance of organic phosphates in muscle physiology. The interpretation, that the observed increase in inorganic phosphates as well as the formation of lactic acid during muscular contraction came from a hexosephosphate, lactacidogen, was apparently in error. Lohmann<sup>5</sup> later (1928) showed that, by the method used by Embden, the orthophosphate yield came mostly from the splitting of pyrophosphate and only in small part from the lactacidogen, and

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that nucleotide pyrophosphate was an important compound in muscle metabolism. Lohmann noted distinct decrease in pyrophosphate on contraction and also noted that the pyrophosphate was linked to adenylic acid. The splitting off of ammonia ( $\text{NH}_3$ ) in muscle contraction was found by Embden and Zimmermann<sup>6</sup> and by Parnas and Mozolowski<sup>7</sup> to come from adenylic acid. Embden correlated the endurance of muscle for prolonged contraction with its phospholipid content.

Lundsgaard's halogen acetic acid experiments<sup>8</sup> proved that muscle work is possible, and consequently that the chemical processes of contraction may occur, without the formation of lactic acid. This relegated lactic acid formation to a secondary position and fitted in with the observations of Embden and his coworkers that the pH of the muscle changed to the alkaline side, not to the acid side, at the instant of contraction.

Fiske and Subbarow,<sup>9</sup> however, clarified the whole matter when they discovered that creatine phosphoric acid as a secondary potassium salt, phosphocreatine, was the active principle that made up part of what had previously been determined as orthophosphate. Eggleton and Eggleton<sup>10</sup> simultaneously identified the active substance as "phosphagen" an unstable form of organic hexosephosphate, a phosphoric ester of glycogen, or a precursor of both lactacidogen and lactic acid. Later these authors acknowledged "phosphagen" to be creatine phosphoric acid or phosphocreatine. Nevertheless, glycogen-lactic acid metabolism is essential, supplying as it does the energy for phosphocreatine resynthesis, while the intermediary products as hexosephosphate act as buffers.

Embden and Lehnartz<sup>11</sup> had emphasized the reversible phosphate breakdown and rebuilding in recovery, with decrease of the synthesis in fatigued muscle. Fiske and Subbarow<sup>9</sup> determined that the phosphocreatine-glycogen ratio in skeletal muscle remained fairly constant: both decreasing equally under aerobic conditions, while in anaerobiosis the phosphocreatine disappears more rapidly than the glycogen and the ratio falls. Phosphocreatine was found to be relatively stable in an alkaline medium, yet it hydrolyzed with increasing velocity as the pH rose. A lactic acid acidosis results in a loss of creatine and of potassium from the muscle cells. Creatine, phosphates and potassium were thus established, along with glycogen and lactic acid, in skeletal muscle physiology. With these facts before them it was logical for investigators to apply the same methods to the study of heart muscle physiology.

Vollmer<sup>12</sup> found phosphocreatine constituting from 75 to 80 per cent of the total creatine content of the resting ventricular muscle of the slow beating thin-walled turtle heart. He noted that the phosphocreatine dropped to from 20 to 25 per cent of the total creatine after

contraction. Pollack, Flack, Essex and Bollman<sup>13</sup> have made similar, but technically much more difficult, studies of phosphocreatine in dogs' hearts from the Starling heart-lung preparations. The failure of these investigators to confirm Vollmer's findings may be due in large measure to the difficulties inherent in mammalian heart studies, namely, the inability to freeze the muscle in the desired phase of contraction.

#### HUMAN HEART MUSCLE CREATINE STUDIES

The experimental studies as to the creatine and phosphocreatine changes in cardiac muscular contraction seemed to indicate that processes similar to those of skeletal muscle physiology were at work. Renewed interest was aroused by these reports in the problems of human heart function. Constabel's findings were recalled and extended by Vollmer and others and various other chemical studies were undertaken. Wilkens and Cullen<sup>14</sup> noted a decrease in total phosphorus and potassium in the heart muscle from patients who had died in congestive failure. Scott,<sup>15</sup> with material supplied him by one of us, confirmed the potassium loss. Seecof, Linegar and Myers<sup>16</sup> followed up Constabel's and Vollmer's studies of the creatine content and reported the creatine values for the various parts of 102 human hearts. They found the left ventricular muscle to contain uniformly more creatine than the right, with a mean of 243 mg. per cent for the left and 188 mg. per cent for the right, averages of 211 and 148 mg. per cent, respectively, and ranges of from 116 to 369 as against 93 to 283 mg. per cent. Vollmer had reported the left ventricle to contain 221 mg. per cent and the right 173 mg. per cent—a 20 per cent difference—whereas Constabel had elicited only a 10 per cent difference.

Cowan<sup>17</sup> has supplied corroborative evidence of Constabel's early contention that lowered total myocardial creatine values were found in hearts that had been seriously damaged. In 11 of 17 hearts from patients who had died in congestive failure, he recorded total creatine values of from 92 to 152 mg. per cent. These figures are low as compared with those found in "normal" hearts (from patients who had died of other causes) which showed mean values of 202 mg. per cent  $\pm$  37.

Under our direction in this laboratory W. O. Brown, Jr., analyzed, as our first series,<sup>18</sup> the left ventricular muscle from 50 adults, kindly supplied us from autopsies by Dr. Tom Oliver, Dr. Jarrett Williams and Dr. Sion Holley, of the staff of the Department of Pathology. Thirteen of the 50 hearts were from patients with congestive failure and in these the creatine values ranged from 85 to 132 and averaged 111 mg. per cent, whereas in 10 hearts from patients with syphilitic aortic disease, the values ranged from 110 to 137, and averaged 123



mg. per cent. In a miscellaneous group without gross heart disease the creatine values ranged from 123 to 205, with an average of 150 mg. per cent.

## PRESENT STUDIES

A second series of 105 human hearts, in which the left ventricular muscle has been analyzed in our laboratory,\* furnishes the basis for this paper. The creatine values in this second and larger group of hearts correspond quite closely to the previously reported findings, but they will be set down in detail as a matter of record.

TABLE I  
CREATINE CONTENT OF NORMAL HUMAN HEARTS  
(SECOND SERIES)

AGE	SEX	RACE	HT. WT.	CR. (MG. %)	SOLIDS %	DR. CR. (MG. %)
<i>A. Death From Trauma</i>						
31	M	W	310	145	21.8	666
18	M	W	275	176	20.4	863
50	M	W	340	169	20.1	840
16	M	B	180	196	20.0	980
55	M	W	110	173	20.6	838
58	M	W	375	183	20.9	875
38	M	B	300	180	21.2	847
29	M	W	290	210	20.0	1050
45	M	B	350	187	20.7	900
48	F	W	210	212	21.6	982
57	M	W	390	185	20.3	912
				183	20.7	887
				±17	±0.62	±79
<i>B. Death From Infectious Disease</i>						
69	M	W	350	175	20.7	845
43	M	W	300	156	18.6	838
45	M	W	200	171	20.0	855
80	F	W	300	155	18.6	832
48	M	W	440	172	20.1	858
13	F	B	125	209	21.9	955
49	M	W	365	250	22.6	1105
43	F	W	220	168	19.3	872
26	M	W	285	163	19.8	823
40	M	W	300	187	20.2	930
36	M	W	340	176	20.0	878
9	F	W	115	159	20.1	790
59	M	W	390	184	20.2	910
43	M	B	330	180	21.1	855
36	F	B	200	191	20.6	910
72	M	W	400	185	20.6	900
56	F	B	175	145	19.3	752
38	M	B	250	151	20.6	733
35	F	W	320	150	23.4	641
25	F	W	265	149	20.4	730
21	F	W	185	155	18.1	858
24	F	B	250	161	18.7	864
				172	20.1	858
				±15.4	±0.96	±70
				175	20.3	868
				±20.7	±0.87	±76

\*These analyses were made by Peter S. Erhard.

The results were tabulated according to the clinical and post-mortem data under the headings: 1, apparently normal hearts; 2, grossly abnormal hearts that had not shown failure; 3, hearts from patients dying of congestive cardiac failure; and 4, infarcted hearts from patients with coronary thrombosis.

*Group 1.*—There were 34 hearts which were apparently normal, the analyses of the left ventricular muscle of which showed an average

TABLE II  
HEART DISEASE WITHOUT FAILURE

AGE	SEX	RACE	HT. WT.	CR. (MG. %)	SOLIDS %	DR. CR. (MG. %)
<i>A. With Hypertension</i>						
72	M	B	400	221	21.6	1022
68	M	B	510	204	20.8	989
38	M	B	510	158	19.4	814
68	M	W	540	199	20.1	992
48	M	B	645	198	21.1	937
45	M	B	410	207	19.5	1063
				198	20.4	970
<i>B. With Coronary Sclerosis</i>						
73	M	W	335	144	19.7	731
60	M	W	325	148	21.4	690
53	M	W	295	176	19.4	907
67	M	W	250	119	19.2	622
89	M	W	325	137	19.7	695
60	M	W	475	143	18.8	761
45	M	W	350	187	20.8	900
72	M	W	320	175	20.5	853
45	M	B	260	159	19.2	831
70	M	W	230	175	21.5	815
64	M	W	285	162	20.2	800
				157	20.0	783
<i>C. With Rheumatic Aortic and Mitral Disease</i>						
41	M	B	450	210	19.9	1058
				173	20.1	860
SEVERE ANEMIAS						
43	M	B	290	144	17.2	837
55	M	W	425	137	19.7	735
67	M	W	250	119	19.2	622
29	M	W	290	210	20.0	1050
72	F	W	320	175	20.5	853
				157	19.3	819
GLOMERULONEPHRITIS WITH UREMIA						
43	F	W	435	150	19.6	785
49	F	B	400	169	20.0	845
48	M	B	400	146	20.7	706
40	F	B	280	165	21.8	756
45	M	B	260	159	19.2	831
39	F	B	420	168	22.0	763
				159	20.3	781

total creatine content of 175 mg. per cent  $\pm$  20.7 total solids of 20.3 per cent  $\pm$  0.877, and dried muscle values of 868 mg. per cent  $\pm$  70 (Table I).

*Group 2.*—A series of 30 hearts from patients with heart disease, but without heart failure, presented creatine values that averaged about the same as those of the normal hearts, namely, 173 mg. per cent, 20.1 per cent, and 860 mg. per cent. Of these, one from a patient with rheumatic aortic regurgitation and mitral disease was found to contain 210 mg. per cent creatine, 19.9 per cent solids, and 105.8 mg. per cent in dried left ventricular muscle.

Six hearts from patients with hypertension, but not in failure, showed an average of 198 mg. per cent  $\pm$  15.6 of creatine, 20.4 per cent of solids, and 970 mg. per cent  $\pm$  79 of dried muscle; while 11 with coronary sclerosis alone averaged 157 mg. per cent creatine, 20 per cent solids, and 783 mg. per cent dried muscle.

In the left ventricular muscle of hearts from six patients who died in uremia with glomerulonephritis the creatine value averaged 159 mg. per cent, the solids, 20.3 per cent and the dried muscle, 781 mg. per cent; the values in five cases of severe anemia averaged 157 mg. per cent in creatine, 19.3 per cent in solids and 819 mg. per cent in dried muscle (Table II).

*Group 3.*—Of particular interest to us is the small series of four hearts from patients who died following acute coronary thrombosis. In these the heart muscle from the region of the infarct uniformly showed striking losses of creatine when compared with the uninfarcted myocardium. In most instances the relation was about 2 to 1. In these hearts the creatine level in the uninfarcted muscle was also

TABLE III

## A. CORONARY OCCLUSION

HT. WT.	CREATINE (MG. %)		SOLIDS (%)		DRIED (MG. %)	
	GOOD	INFARCTED	GOOD	INFARCTED	GOOD	INFARCTED
610	122	41	23.45	18.0	520	228
550	104	61	21.95	15.05	497	405
800	100	52	19.7	18.2	558	318
900	151	31	19.15	17.25	788	180

## B. SEVERE PROLONGED AND COMPLICATED INFECTIOUS DISEASES

HT. WT.	CREATINE (MG. %)	SOLIDS (%)	DRIED (MG. %)
340	101	18.2	556
375	131	22.0	596
385	111	23.0	482
375	129	19.0	681
259	110	19.1	577
300	101	22.6	448
350	136	21.1	645
300	143	22.4	641
340	139	19.6	710
270	114	18.4	623
	121	20.5	596

reduced to about the same concentrations found in the hearts of patients with congestive failure (Table III, A).

Ten hearts from patients with prolonged and complicated infectious diseases, with microscopic evidence only of myocardial damage, presented similarly low creatine figures, averaging 119 mg. per cent, with 20.8 per cent solids and 671 mg. per cent in terms of dried weight (Table III, B).

*Group 4.*—Thirty-two hearts from patients who had died in congestive failure were found upon analysis to contain about 30 per cent less creatine than normal with the following values for the left ventricular myocardium: creatine, 122 mg. per cent  $\pm$  20.8; solids, 20.3  $\pm$  1.2 per cent; and dried weight, 605 mg. per cent  $\pm$  100 (Table IV).

These values corroborate our previous reports and those of others except for the ten low values found in infectious diseases of a chronic and complicated type, as shown in Table III, B.

TABLE IV

CREATINE CONTENT OF HEARTS FROM PATIENTS DEAD OF CONGESTIVE FAILURE  
(SECOND SERIES)

AGE	SEX	RACE	ETIOLOGY	HT. WT.	FRESH (MG. %)	SOLIDS (%)	DRIED (MG. %)
58	M	W	Hypertension + C.O.*	550	130	21.10	617
45	M	B	Sclerosis	520	106	20.70	512
20	M	W	Hypertension	820	154	21.1	738
70	M	B	Coronary sclerosis	560	85	18.7	453
45	F	B	Hypertension	650	95	19.1	497
34	F	B	Syphilis	560	118	20.4	577
63	M	W	Sclerosis	440	140	19.3	723
50	M	B	Syphilis	540	120	20.0	600
39	F	B	Hypertension	475	100	18.6	537
50	M	W	Syphilis	850	135	20.05	673
55	M	W	Hypertension	600	112	19.9	563
68	M	W	Sclerosis	375	130	21.0	618
73	M	B	Sclerosis	345	125	20.0	625
57	M	W	Hypertension + C.O.	610	103	18.3	562
50	F	B	Hypertension	610	132	20.1	657
54	M	W	Syphilis + Anemia	425	137	19.7	696
59	M	W	Hypertension + C.O.	700	122	23.4	520
76	M	W	Hypertension	580	109	20.5	532
30	M	B	Sclerosis + C.O.	375	145	20.5	705
50	M	B	Hypertension	540	165	21.0	785
67	M	B	Hypertension	650	109	19.1	572
41	M	W	Hypertension	460	133	20.5	649
60	M	W	Sclerosis + C.O.	350	104	21.9	497
69	M	B	Hypertension + C.O.	800	110	19.7	558
50	M	B	Syphilis + C.O.	900	151	19.1	788
75	F	B	Hypertension	500	144	20.8	690
65	M	B	Hypertension	495	138	20.7	607
49	M	B	Syphilis	650	112	23.4	478
56	M	B	Hypertension	600	100	21.7	457
70	F	W	Hypertension	430	130	21.7	598
32	M	B	Syphilis	400	91	17.8	511
65	M	B	Hypertension	340	139	19.6	710
Averages					122	20.3	605
					$\pm 20.8$	$\pm 1.22$	$\pm 100$

\*C.O., coronary occlusion.

Cowan did not find low creatine values as the result of infectious diseases, but Constabel reported figures quite similar to ours. In fact, our normals are distinctly below those reported by Cowan, but again agree with Constabel's normal levels (Table V).

TABLE V  
CREATINE CONTENT OF HUMAN HEARTS

NO.	CAUSE OF DEATH	FRESH (MG. %)	SOLIDS (%)	DRIED (MG. %)
11	Traumatic	183 ± 17.0	20.7 ± 0.62	887 ± 79
23	Infections	172 ± 15.4	20.1 ± 0.98	858 ± 70
24	Controls	175 ± 20.7	20.3 ± 0.87	868 ± 70
1	Heart disease without failure			
	Rheumatic, aortic, and mitral	210	19.9	1058
6	Hypertension	198 ± 15.6	20.4	970 ± 79
11	Coronary sclerosis	157	20.0	783
18	Total without failure	173	20.1	860
6	Glomerulonephritis with uremia	159	20.3	781
5	Severe anemia	157	19.3	819
32	Congestive heart failure	122 ± 20.8	20.3 ± 1.2	605 ± 100
10	Infections with microscopic myocardial change	121	20.5	596

#### CONCLUSIONS

The results of our studies, and those of others, convince us that low human myocardial creatine values are more or less constant accompaniments of congestive failure and must be among the significant chemical changes that are associated with myocardial damage and insufficiency. Particularly significant are the extremely low total creatine contents of the myocardium from the infarcted areas in cases of coronary thrombosis.

#### REFERENCES

1. Christian, H. A.: *Speculations on Some Problems of Cardiac Failure*, South. M. J. 20: 28, 1927.
2. Constabel, Fr.: Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszustanden, *Biochem. Ztschr.* 122: 152, 1921.
3. Pekelhering, C. A., and Van Hoogenhuyze, C. J. C.: Die Bildung des Kreatins im Muskel beim Tonus und bei der Starre, *Ztschr. f. physiol. Chem.* 64: 262, 1910.
4. Embden, G., and Lawaczek, H.: Ueber die Bildung anorganischer Phosphorsäure bei der Kontraktion des Frostmuskels, *Biochem. Ztschr.* 127: 181, 1922.
5. Lohmann, K.: Ueber das Vorkommen und den Umsatz von Pyrophosphat in Zellen. I. Nachweis und Isolierung des Pyrophosphats, *Biochem. Ztschr.* 202: 466, 1928.
6. Embden, G., and Zimmermann, M.: Ueber die Bedeutung der Adenylsäure für die Muskelfunktion, *Ztschr. f. physiol. Chem.* 167: 127, 1927.
7. Parnas, J. K., and Mozolowski, W.: Ueber den Ammoniakgehalt und die Ammoniakbildung im Muskel und deren Zusammenhang mit Funktion und Zustandsänderungen, *Biochem. Ztschr.* 184: 399, 1927.
8. Lundsgaard, E.: Untersuchungen ueber Muskelkontraktionen ohne Milchsäurebildung, *Biochem. Ztschr.* 217: 162, 1930.

9. Fiske, C. H., and Subbarow, Y.: Phosphocreatine, *J. Biol. Chem.* 81: 629, 1929.
10. Eggleton, P., and Eggleton, G. P.: A Method of Estimating Phosphagen and Some Other Phosphorous Compounds in Muscle Tissue, *J. Physiol.* 68: 193, 1929.
11. Embden, G., and Lehmann, E.: Ueber die Bedeutung von Ionen für die Muskelfunktion, *Ztschr. f. physiol. chem.* 134: 243, 1924.
12. Vollmer, N. Z.: Untersuchungen ueber den Kreatin und Phosphorsäuregehalt verschiedener Herzteile, *Ber. d. ges. Phys. u. exper. Pharmacol.* 51: 505, 1929.
13. Pollack, H., Flack, E., Essex, H. E., and Bollman, J. L.: Phosphorus Compounds in the Perfused Heart of the Dog, *Am. J. Physiol.* 110: 97, 1934.
14. Wilkens, W. E., and Cullen, G. E.: Electrolytes in Human Tissue, *J. Clin. Investigation* 12: 1063, 1933.
15. Scott, L. C.: The Determination of Potassium in Cardiac Muscle, *J. Clin. Investigation* 10: 745, 1931.
16. Seecof, D. P., Linegar, C. R., and Myers, V. C.: The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, *Arch. Int. Med.* 53: 574, 1934.
17. Cowan, D. W.: The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, *AM. HEART J.* 9: 378, 1934.
18. Herrmann, George: Some Biochemical Factors in Heart Failure, Medical Papers dedicated to Henry Asbury Christian, Waverly Press (1936) 17-33, and *South. M. J.* 29: 386, 1936.

# THE EFFECT OF POTENTIAL VARIATIONS OF THE DISTANT ELECTRODE ON THE PRECORDIAL ELECTROCARDIOGRAM\*

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THE most important of the controllable factors that influence the form of the precordial electrocardiogram may be listed as (1) the location of the exploring† electrode, (2) the size of the exploring electrode, and (3) the potential of the indifferent‡ electrode. The effect of the first has already been adequately demonstrated by the extensive work of Wilson and his associates.<sup>1-5</sup> The second will be taken up in a later publication. It is the purpose of this article to emphasize the significance of the potential of the distant electrode in the determination of the form of the curve obtained when the exploring electrode is placed over the precordium.

Leads IV, V, and VI as described by Wood, Bellet, McMillan, and Wolferth<sup>6</sup> are suitable for an analysis of this type because they serve to bring out some very obvious, though apparently not very well known, relationships. In taking these leads, the right arm electrode is placed on the precordium in the vicinity of the apex, the left arm electrode on the back at a point just medial to, and below, the inferior angle of the left scapula, and the left leg electrode on the left leg. By pairing in succession, the precordium with the back, the precordium with the left leg, and the back with the left leg, Leads IV, V, and VI, respectively, are obtained. By joining each pair with a straight line it is easy to visualize a triangle laid out in the sagittal plane of the body to the left of the midline. Roughly, this triangle is equilateral, but whether it be regarded so or not, it can easily be shown that Lead V equals Lead IV plus Lead VI. The simple principle upon which this rule depends is the same as that upon which Einthoven's law that Lead II equals Lead I plus Lead III also depends. This principle, recently discussed by Wilson, Macleod and Barker,<sup>7</sup> is that the difference in potential between two points is the

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†The terms "exploring" and "indifferent" are synonymous with "near" and "distant" as applied to the electrodes in these leads from two points on the body one of which is close to, and the other removed from, the heart.

same as the algebraic sum of the differences in potential between each of these points and a third one. Clearly, the law holds regardless of the shape of the triangle formed by connecting the three points. However, with the new leads the size and the direction of the electrical axis in the sagittal plane cannot be calculated as in the frontal plane with Einthoven's triangle, for at least two reasons: first, because the source of potential is eccentrically placed in the sagittal triangle so that the precordial electrode is much closer to this source than either of the other two electrodes. In the case of Einthoven's triangle the geometric and trigonometric formulas used in the determination of the size and the direction of the electrical axis are based upon the fundamental assumption that the electrical forces generated by the heart are located at the center of the triangle. This is the same as saying that these formulas can be used only when the three points of leading in any plane are equidistant, or distant\* from the heart. Second, the precordial electrode will be influenced most by those muscle elements of the heart closest to it. This is easily deduced from the change in the contour of the ventricular complex as the exploring electrode is placed on various parts of the exposed animal<sup>3, 10, 11, 13</sup> or human<sup>12</sup> heart, or on various parts of the intact animal<sup>10, 13</sup> or human<sup>2, 5, 10</sup> precordium. Because of the nature of the laws governing currents in volume conductors, those muscle elements close to the exploring electrode will cause large variations in its potential, compared with the effects of the entire heart on the distant electrode placed either on the dorsum or the left leg. The electrical variations of the first, therefore, will largely determine the form of the curve obtained.

This second point brings out a serious disadvantage of any system of leading from two points on the body, one of which is near to, and the other distant from, the heart. It is impossible to say, from an inspection of the curves obtained, which deflections arise from the potential variations of the exploring electrode, and which from the potential variations of the indifferent one. However, the former may be freed of the effects of the latter, as demonstrated by Wilson and his associates, either indirectly by calculation, or directly by making use of an indifferent electrode known to be at zero potential.

Wilson<sup>9</sup> showed that the potential  $V$  of any apex of Einthoven's triangle is proportional to the cosine of the angle  $\theta$  made by the electrical axis with the line drawn from the center of the triangle to the

\*Distant as well as equidistant, because the potential of a point in an infinite, homogeneous conducting medium varies inversely as the square of the distance between this point and the source of the potential. As this distance is increased, the corresponding fall in potential of the point in question becomes negligible. For practical purposes the human body may be regarded as a large, homogeneous, conducting medium (see Wilson, Einthoven).



apex in question. By converting  $\theta$  into terms of  $\alpha$  (the angle made by the electrical axis with the horizontal) Wilson, Macleod, and Barker<sup>14</sup> obtained an expression for the potential of the left leg, namely,

$$V_F = \frac{e_2 + e_3}{3},$$

where  $e_2$  and  $e_3$  represent simultaneous deflections in standard Leads II and III. With the aid of this expression it is easy to see how similar ones for the potential of the precordium and of the back, in terms of both the standard and the special leads, may be obtained.

If  $e_4$ ,  $e_5$ , and  $e_6$  represent the deflections in Leads IV, V, and VI, respectively, and  $V_P$ ,  $V_B$ , and  $V_F$ , the potentials of the precordium, the back, and the left leg (apices of the sagittal triangle), then

$$*e_4 = V_B - V_P \quad (1)$$

$$e_5 = V_F - V_P \quad (2)$$

$$e_6 = V_F - V_B \quad (3)$$

Since, as was shown, and will be further demonstrated, Lead V equals Lead IV plus Lead VI,

$$e_5 = e_4 + e_6 \quad (4)$$

$$\text{and } (V_F - V_P) = (V_B - V_P) + (V_F - V_B) \quad (5)$$

Two expressions for the precordial potential and one for the back potential are therefore:

$$-V_P = e_4 - V_B \quad (6)$$

$$-V_P = e_5 - V_F \quad (7)$$

$$-V_B = e_6 - V_F \quad (8)$$

In terms of five of the six leads, these become:

$$-V_P = e_4 + \left\{ e_6 - \frac{e_2 + e_3}{3} \right\} \quad (9)$$

$$-V_P = e_5 - \frac{e_2 + e_3}{3} \quad (10)$$

$$-V_B = e_6 - \frac{e_2 + e_3}{3} \quad (11)$$

It is entirely unnecessary to calculate potentials in this manner, however, since they may be simply and rapidly obtained by the direct method first described by Wilson, Macleod, and Barker in 1932, and further elaborated in 1934.<sup>1</sup> With this direct method an attempt has been made to demonstrate the quantitative and qualitative effects of the potential variations of a distant electrode on the curve obtained when this electrode is paired with one on the precordium, as is done in Leads IV or V of Wolferth and his associates.

\*The minus sign is placed before  $V_P$  in Leads IV and V because the more negative (electrically speaking) the potential of the precordium compared to the back and left leg, the more positive (directionally speaking) will be the corresponding deflection in these leads. Similarly, the more negative the back with respect to the left leg, the higher will be the deflections in Lead VI.

## METHOD

Nine subjects whose standard electrocardiograms showed widely varying electrical axes in the frontal plane were selected. The clinical diagnoses in these and a brief summary of each are given in Table I. The essential electrocardiographic features in the standard leads were as follows: atypical right bundle-branch block in two; left bundle-branch block in one; a deep Q in Lead I with a QRS interval of 0.114 sec. in one; a  $Q_1T_1$  type of curve associated with infarction of the anterior wall of the heart in two, one of which also showed a QRS interval of 0.110 sec.; one each of right and of left deviation of the electrical axis with QRS intervals less than 0.1 sec.; and, finally, one electrocardiogram normal in all respects except for slight deviation of the electrical axis to the left.

On each subject a series of nine electrocardiograms were taken simultaneously with standard Lead I in the following order: three standard leads with the galvanometer string at normal sensitivity (1 cm. equals 1 mv.); Leads IV, V, and VI of Wood and Wolferth; and finally the potentials of the precordium ( $V_P$ ), the back ( $V_B$ ), and of the left leg ( $V_F$ ). In order to have comparable curves, the last six, with one exception, were taken with the galvanometer string at half-normal sensitivity (1 cm. equals 2 mv.). All curves were taken with the patients in the sitting position. Leads IV, V, and VI were taken in the usual way. The right arm electrode was placed in the fifth intercostal space in the left midclavicular line, the left arm electrode just medial to, and below, the inferior angle of the left scapula with the patient's arm at his side, and the left leg electrode on the left lower leg. The potentials of these three points were then obtained by pairing each in succession with an indifferent electrode, connected through separate, fixed, noninductive resistances of 5,000 ohms to the right arm, the left arm, and the left leg, respectively. The potential of such an electrode has been proved by Wilson, Johnston, Macleod, and Barker<sup>1</sup> to be practically at zero potential throughout the cardiac cycle. The mechanics in taking the potentials were such that in the finished record positivity of the exploring electrode was represented by a downward deflection. Early in the experiments it was learned that the precordial electrode had to be held at precisely the same point while recording Lead IV, Lead V, and the potential of the precordium ( $V_P$ ), for otherwise the relationships discussed above did not hold. This fact emphasizes the marked effects on the precordial electrocardiogram of even the slightest movement of the exploring electrode.

The electrodes used on the extremities were of German silver wrapped in flannel wet with saturated saline. On the precordium and back the electrodes consisted of a piece of sponge soaked in

TABLE I  
SUMMARY OF CASES STUDIED

CASE NUMBER AND INITIALS	AGE	SEX	COLOR	RECEIVING DIGITALIS	ESSENTIAL FEATURES OF STANDARD ELECTRO-CARDIOGRAMS	Q <sub>r</sub> T <sub>r</sub> type	CARDIAC DIAGNOSIS*
1 J. R.	59	M	W	No			(a) Arteriosclerosis and unknown (b) Enlarged heart, coronary sclerosis, thrombosis of left coronary artery, recent infarction of myocardium (c) Regular sinus rhythm (d) Ifa
2 M. F.	55	M	W	Yes	Atypical right bundle-branch block with tall R and deep, broad S in Lead I. QRS interval of 0.160 second		(a) Hypertension and arteriosclerosis (b) Enlarged heart, arteriosclerosis with dilatation of aorta (c) Regular sinus rhythm, atypical right bundle-branch block (d) Ifb
3 O. P.	37	M	B	Yes	Left deviation of electrical axis T-waves inverted in Leads I and II		(a) Hypertension and syphilis (b) Enlarged heart, aortitis with aneurysm of aortic arch (c) Regular sinus rhythm, pulsus alternans (d) Ifb
4 S. S.	53	M	W	Yes	Left bundle-branch block. Low, vibratory, ventricular complexes in all three leads. QRS interval of 0.174 second		(a) Arteriosclerosis and hypertension (b) Enlarged heart, coronary sclerosis, arteriosclerosis with dilatation of aorta (c) Regular sinus rhythm, left bundle-branch block, ventricular premature contractions (d) III

TABLE I—CONT'D

CASE NUM- BER AND INITIALS	AGE	SEX	COLOR	RECEIVING DIGITALS	ESSENTIAL FEATURES OF STANDARD ELECTRO- CARDIOGRAMS		CARDIAC DIAGNOSIS*
					Q, T, type.	QRS interval of 0.110 second	
5 J. O'D.	49	M	W	No			(a) Arteriosclerosis (b) Coronary sclerosis, myocardial fibrosis, thrombosis of left coronary artery, recent infarction of myo- cardium (c) Regular sinus rhythm, incomplete left bundle-branch block, paroxysmal supraventricular tachycardia with ventricular aberration (d) IIa
6 F. O'C.	18	M	W	No	Right deviation of electrical axis		(a) Congenital maldevelopment (b) Pulmonary stenosis (c) Sinus arrhythmia (d) I
7 E. C.	52	M	W	No	Atypical right bundle-branch block. Prominent R, shal- low, broad S in Lead I. QRS interval of 0.122 sec.		(a) Arteriosclerosis, previous hypertension, emphysema (b) Enlarged heart, arteriosclerosis with dilatation of aorta (c) Sinus tachycardia, atypical right bundle-branch block (d) IIa
8 F. P.	70	F	W	No	Deep Q in Lead I. Left de- viation of electrical axis. QRS interval of 0.114 second		(a) Arteriosclerosis and hypertension (b) Coronary sclerosis, myocardial fibrosis (c) Regular sinus rhythm, incomplete left bundle-branch block (d) IIa
9 D. P.	41	M	W	No	Slight deviation of electrical axis to left		No heart disease

\*Cardiac diagnoses made in accordance with "The Criteria for the Classification and Diagnosis of Heart Disease" of the New York Heart Association.

saturated saline placed in the end of a small test tube where it made contact with a German silver plate. These electrodes had to be held in place by an assistant. Their area of contact with the chest or back was roughly circular, about 1 cm. in diameter.

Two galvanometers were used. One (upper string in illustrations) was a Hindle No. 2 (Cambridge Instrument Co., Inc.) with a string resistance of 4,000 ohms. In circuit with it was a single stage, vacuum tube amplifier,<sup>6</sup> which made it possible to take all special leads without changing the tension of the galvanometer string. The other machine was a Hindle No. 3 (Cambridge Instrument Co., Inc.), also with a string resistance of 4,000 ohms. It was placed perpendicular to the first machine and its string shadow was deflected by means of a plane mirror into the camera slit. In only one instance was parallax present with this arrangement. The second instrument was used in the ordinary way to record standard Lead I at either one-half, three-fifths, or full sensitivity of the string, depending upon the size of the

TABLE II

Values in tenths of a millivolt of deflections in special leads occurring simultaneously with various points in standard Lead I, indicated in the second column. Lead IV, Lead V, and Lead VI are those described by Wood, Bellet, McMillan, and Wolferth.  $V_F$  and  $V_B$  are the potentials of the same points on the precordium and on the back respectively, used in taking Lead IV.  $V_F$  is the potential of the left leg.

CASE NO.	STANDARD LEAD I	LEAD IV ( $V_R-V_F$ )	LEAD V ( $V_F-V_D$ )	LEAD VI ( $V_F-V_B$ )	$V_F$	$V_B$	$V_F$
1	0.035 sec. after peak of Q	17.2	8.2	-10.2	-12.0	5.8	-5.1
	Peak of T	4.2	5.6	1.8	-4.4	0	0.8
2	Peak of R	-9.6	-9.8	0	12.2	0.8	1.5
	Peak of S	3.2	5.2	1.8	-6.6	-2.4	-0.8
	Peak of T	0.5	0	-0.6	-0.2	0.8	0.4
3	Peak of R	-43.6	-45.4	0	46.0	1.6	0.4
	Peak of T	6.0	7.4	0.6	-6.0	0	0.4
4	Peak of R	34.6	23.8	-9.4	-27.4	8.0	-1.8
	End of T	-15.4	-12.0	4.0	12.0	-4.0	0
5	Peak of Q	2.4	3.2	1.4	-2.6	0	0.4
	Peak of R	13.0	0.8	-12.0	-7.2	7.0	-6.8
	Peak of T	-1.4	1.4	3.4	-0.1	-0.5	1.1
6	0.015 sec. after peak of S	22.0	27.2	5.2	-24.8	-1.0	4.2
	Peak of T	-14.6	-13.8	1.8	14.8	0.4	2.8
7	Peak of R	-6.0	-6.0	0	5.2	0	-0.4
	Peak of T	-1.6	-1.6	0	2.0	0.4	0.4
8	Peak of Q	2.2	4.2	2.4	-3.2	-0.6	1.6
	Peak of S	6.4	7.2	0.8	-6.4	-0.4	0
	Peak of T	-6.0	-6.0	0	6.0	0	0
9	Peak of R	-16.8	-16.0	0.4	18.8	1.4	1.6
	Peak of T	-8.0	-6.2	1.0	7.2	-0.2	0.8

\*The authors are indebted to Dr. Franklin D. Johnston, of the University of Michigan Medical School, for designing and constructing this amplifier.

deflections (lower curve in all illustrations). Simultaneous points in various leads were determined with the aid of a comparator designed by Capt. Elliott and manufactured by the Cambridge Instrument Co., Inc. The points selected were those that seemed most likely to show a very high deflection in all special leads, and they varied in each subject (Table II).

Where it was possible to identify the "intrinsic deflection," the time of this with respect to the beginning of the ventricular complex in standard Lead I was measured with the comparator. Used by the same operator, the error with this instrument was not greater than  $\pm .003$  sec.

### RESULTS

Table II shows the values obtained for simultaneous deflections in Leads IV, V, and VI, and for the corresponding potentials of the precordium ( $V_P$ ), the back ( $V_B$ ), and the left leg ( $V_F$ ). In measuring these, it was necessary to select the proper sign before the figures. In the leads taken according to the method of Wood and Wolferth, an upright deflection was positive, and a downward deflection, negative. The reverse, however, was true for the point potentials, because the hook-up to the galvanometer was such that a positive variation in potential was represented in the finished record by a downward movement (see footnote p. 700).

If the columns in Table II headed "Lead IV," "Lead V," and " $V_P$ " are compared, the quantitative effects of the potential variations of the back and of the left leg upon those of the precordium can be seen at a glance. The greatest difference between simultaneous potentials in Lead IV and in  $V_P$  was 0.72 mv. (Case 4). The greatest difference between simultaneous potentials in Lead V and  $V_P$  was 0.64 mv. (Case 5). The mean difference, without regard to sign, in the nine cases between twelve simultaneous, initial ventricular deflections in Lead IV and in  $V_P$  was 0.28 mv. The mean difference between these same deflections in Lead V and  $V_P$  was 0.23 mv. Clearly, the average effect of the indifferent electrode, whether it be on the left leg or on the back, is small; the important point to be emphasized is that this effect is extremely variable.

The qualitative effects of the indifferent electrode are apparent in Figs. 1 to 6. It is very easy to see that in every instance the potential of the precordium ( $V_P$ ) dominated the curve obtained when this point was paired either with the back or the left leg (Lead IV or Lead V). This may not be true, however, if the precordial potential is small (see discussion).

The figures in Table II bear out the truth of the law  $\text{Lead V} = \text{Lead IV} + \text{Lead VI}$ , although in one instance there is a discrepancy

as large as 0.18 mv. (Case 3). Two reasons were most important in determining small differences: first, a point occasionally selected in standard Lead I for measurement was found to be simultaneous with a rapidly changing deflection, almost vertical in extent, in one or several of the special leads. The difficulties in measuring the exact

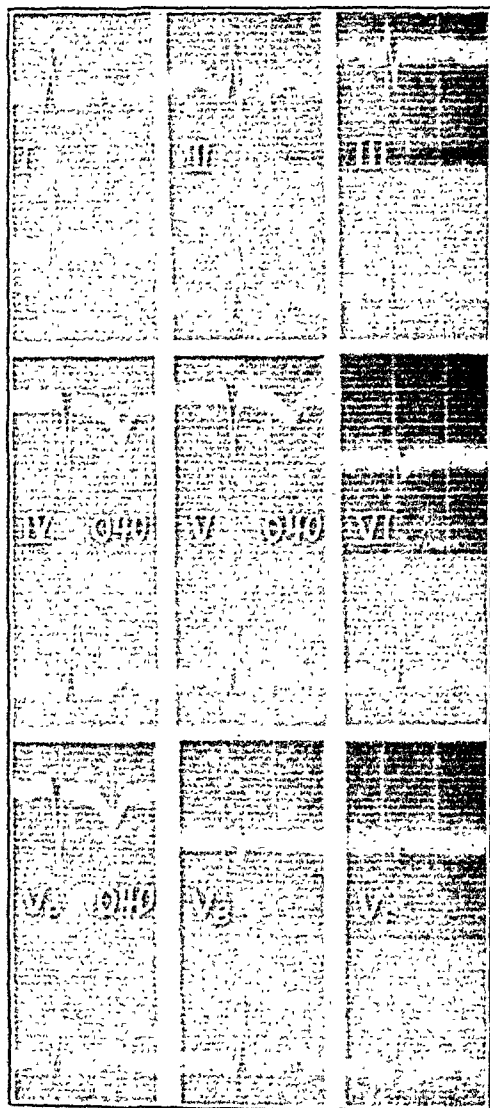


FIG. 1.—Case 9. No heart disease, slight left deviation of the electrical axis. The lower curve in each record is standard Lead I taken with the galvanometer string at normal sensitivity (1 cm. equals 1 mv.). The upper curves in the first three records are, I, standard Lead I; II, standard Lead II; III, standard Lead III. These also were taken with the string at normal sensitivity. The upper curves in the last six records were taken with the string at half-normal sensitivity (1 cm. equals 2 mv.), and are as follows: IV, V, and VI are Leads IV, V, and VI of Wolfersht and his associates.  $V_1$ ,  $V_2$ , and  $V_3$  are the potential variations, determined by the method of Wilson, of the following points:  $V_1$ , the fifth intercostal space in the left midclavicular line;  $V_2$ , the back just medial to, and above, the inferior angle of the left scapula;  $V_3$ , the left leg. Precisely the same points were used in taking Lead IV as in taking the potentials of the precordium ( $V_1$ ) and of the back ( $V_3$ ).

The figures written on the curves give the interval between the first QRS deflection in Lead I, and the beginning of the chief upstroke (intrinsic deflection) in the upper curve.

In all subsequent illustrations, the symbols and figures have the same significance. Unless otherwise stated, the string sensitivity is also the same. The time lines on all curves indicate one-fifth of a second.



Fig. 2.

Fig. 2.\*—Case 6. Congenital pulmonary stenosis, right deviation of the electrical axis. The lower curve (Standard Lead I) in the first record was taken with the galvanometer string at approximately three-fifths normal (1 cm. equals 0.6 mv.). In subsequent curves it is recorded at half its normal amplitude.

Fig. 3.\*—Case 3. Hypertensive and syphilitic heart disease with aneurysm of aorta, left deviation of electrical axis. Lower curves in all records are three-fifths of normal amplitude.

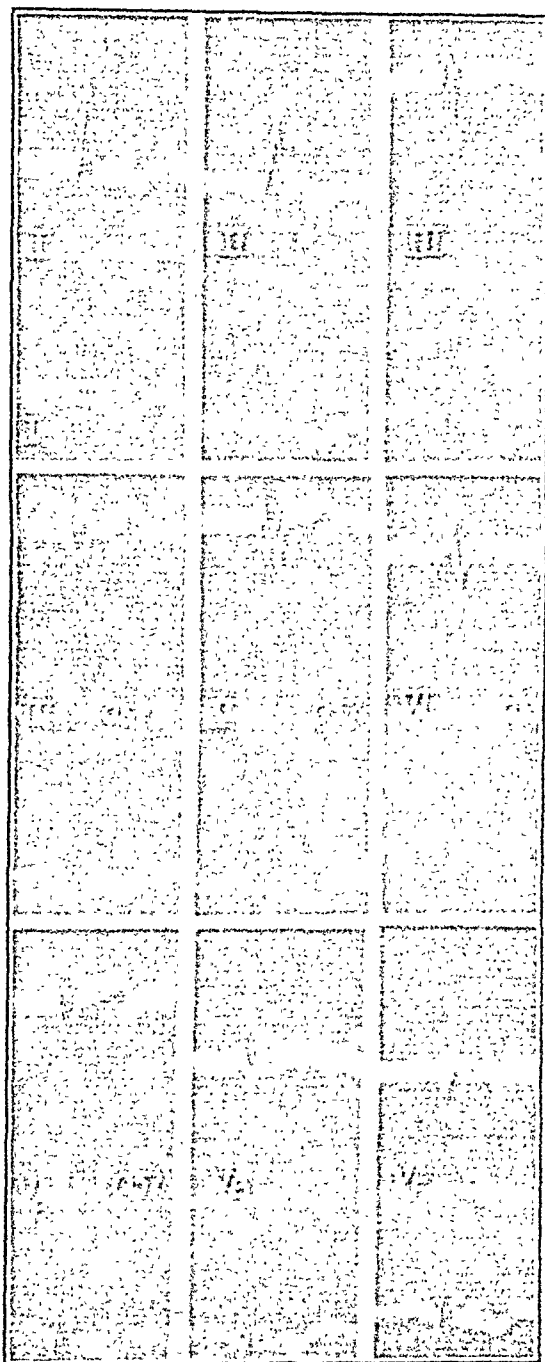


Fig. 3.

\*In the first record of Fig. 2, and also of Fig. 3, it will be noted that although the upper curve was taken with the string at normal sensitivity and the lower one with the string at three-fifths normal; nevertheless the curves have approximately the same amplitude. The reasons for this are twofold: first, the upper string was connected with the output terminals of a vacuum tube amplifier, as described in the text, and the lower string was used in the ordinary way. With this arrangement, when Lead I was taken simultaneously on both strings, short circuiting through the second was such that the amplitude of the deflections recorded by the first was reduced by approximately 30 per cent. Second, it was discovered after completion of these experiments that the resistance box of the lower string was inaccurate. Compared with the deflection caused by a known standard milliamperage, the deflection resulting from movement of the smaller, compensating resistance knob through one division was only nine-tenths as large. Therefore all waves recorded by this string were too large by approximately 10 per cent. When the upper curve was recorded at normal string sensitivity, and the lower at three-fifths normal, it is easy to see how these two factors caused the size of the curves to approach each other.

The amplitude of the special leads was entirely correct, since the resistance box of the galvanometer used to record them was accurate.



size of such a deflection even with the aid of a comparator are not hard to imagine. Second, precordial electrocardiograms, more especially those taken with the exploring electrode close to the apex of the heart, vary with respiration. Although simultaneous points in several ventricular complexes were measured in every case, and a mean value was determined, some error on this score was unavoidable. For similar

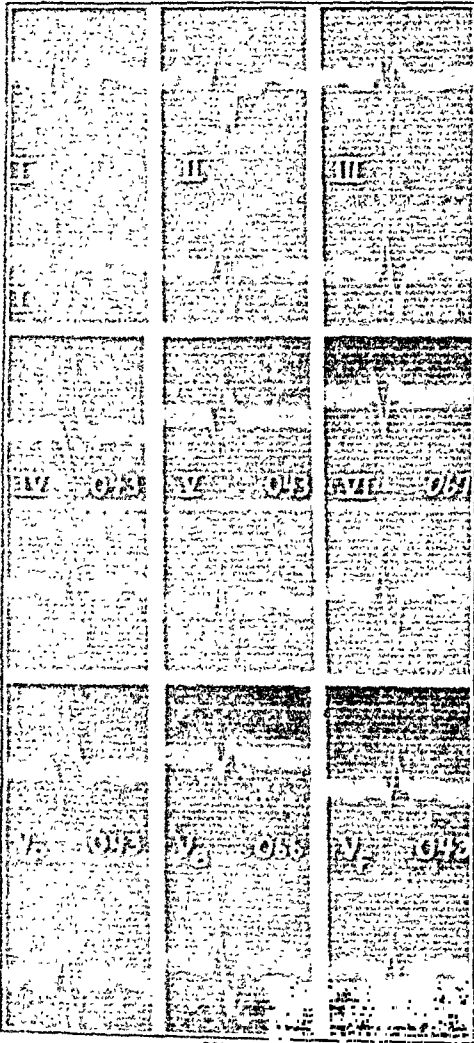


Fig. 4.

Fig. 4.—Case 2. Hypertensive and arteriosclerotic heart disease, atypical right bundle-branch block (QRS interval 0.160 sec.). The potential of the left leg,  $V_R$ , is at normal amplitude rather than at half-normal as are the special leads in the remainder of this and in all other illustrations.

Fig. 5.—Case 4. Arteriosclerotic and hypertensive heart disease, left bundle-branch block (new terminology; QRS interval 0.174 sec.).

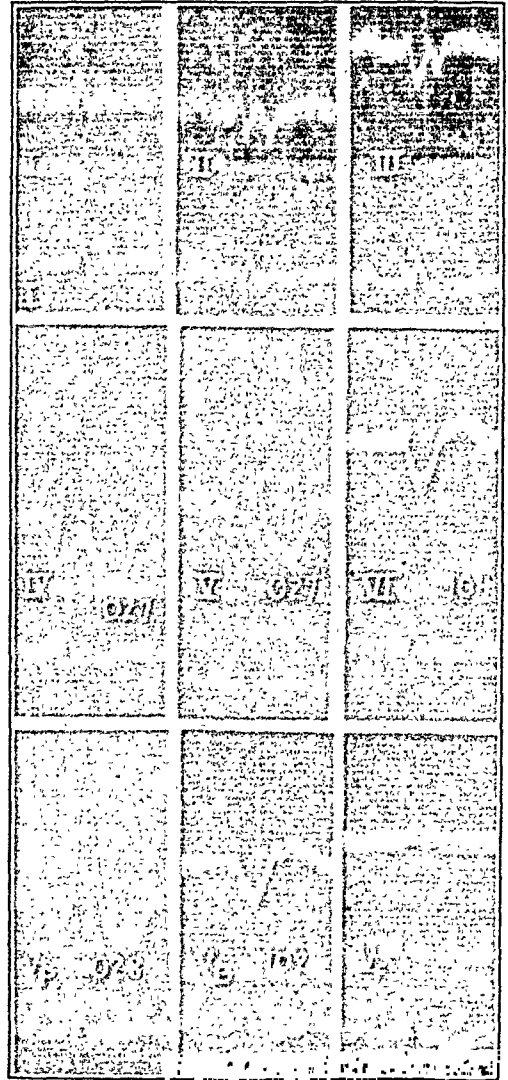


Fig. 5.

reasons Leads IV, V, and VI were not exactly the same as  $(V_R - V_P)$ ,  $(V_T - V_P)$  and  $(V_T - V_R)$ , respectively. A third factor enters here, namely, slight movement of the precordial electrode, which, as has already been pointed out, may cause very marked changes in the curve obtained.

The time of the intrinsic deflection (chief upstroke) of the special leads compared with the earliest initial ventricular deflection in Lead I was measured whenever it could be identified. The results are given

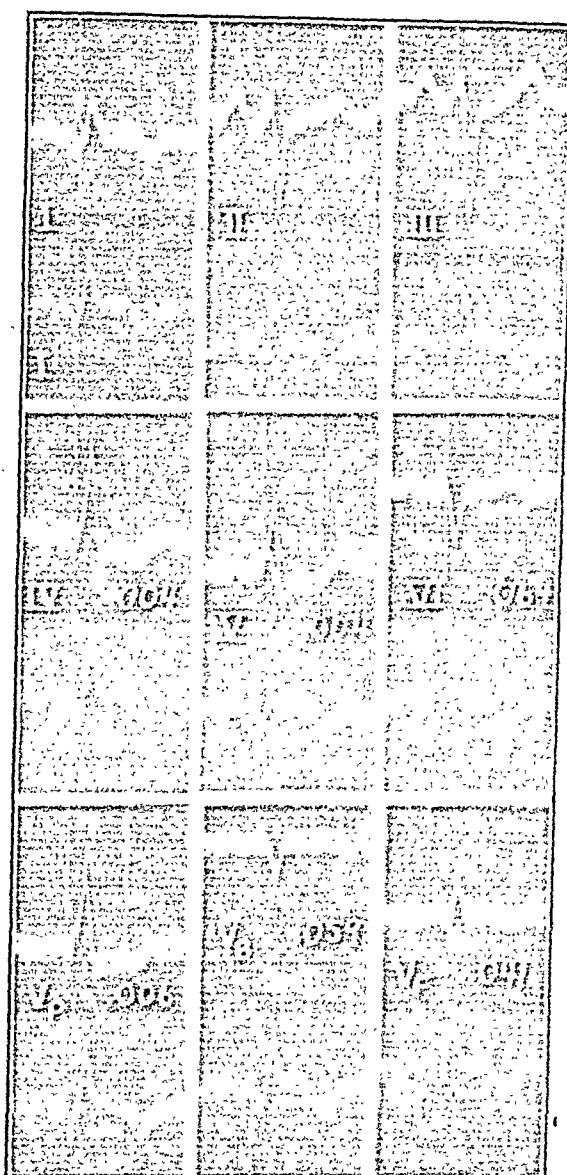


Fig. 6.—Case 5. Recent infarction of the anterior wall of the left ventricle. QRS interval 0.110 sec.

TABLE III

Intervals between the intrinsic deflection (chief upstroke) of the special leads and the earliest, initial, ventricular deflection in standard Lead I. The symbols have the same significance as in Table II.

CASE NO.	IV	V	VI	V <sub>F</sub>	V <sub>F</sub>	V <sub>F</sub>
1	0.009	0.005	0.054	0.006	0.055	0.034
2	0.043	0.043	0.067	0.013	0.066	0.043
3	0.052	0.052	0.064	0.052	—	—
4	0.027	0.027	0.104	0.028	0.102	—
5	0.004	0.004	0.061	0.006	0.059	0.041
6	0.028	0.028	0.066	0.028	—	0.042
7	0.038	0.038	0.049	0.036	—	—
8	0.029	0.032	0.048	0.020	—	0.020
9	0.040	0.040	—	0.040	—	—

in Table III. In Lead IV, Lead V, and  $V_P$ , the chief upstroke began at practically the same time. Apparently the time of this deflection in the first two was not influenced by electrical variations of the distant electrode, for it will be noted that the chief upstroke was usually later in  $V_F$  and  $V_B$  than in  $V_P$ . When the intrinsic deflection could be identified in  $V_B$ , its time was approximately the same as that of the analogous deflection in Lead VI.

#### DISCUSSION

It is not meant to imply that the many methods of taking precordial electrocardiograms now in use are not of diagnostic value to those familiar with the normals of such methods. Few of these, however, have established a standard size for the exploring electrode, or a definite location for it on the precordium, both of which factors have a tremendous influence on the electrocardiograms obtained. Furthermore, by all of these methods, leads are taken from two points on the body, the resulting curve representing the difference in potential between them. Since one point is usually closer to the heart than the other, it is impossible to determine, by inspection of the curve, the size or direction of the potential variations of either. It would seem that if additions are to be made to our knowledge of the electrophysiology of the heart, the method of approach must be simplified so that the potential of a single point can be studied, rather than the difference in potential between two points. All this was very well known to Wilson and his associates when they designed the method used to carry out the work reported here.

It has been pointed out repeatedly by Wolferth<sup>6, 16</sup> and by Roth<sup>17</sup> that although Leads IV and V usually resemble each other, this is not always true. From what has been presented, the reason seems obvious. When discrepancies occur, they are due to considerable differences in the potential variations of the back compared with those of the left leg, provided that the precordial electrode has not been moved while taking these two leads. Theoretically, this should be most common in patients with myocardial infarction near the base of the anterior wall of the left ventricle.

Case 5,\* Fig. 6, is an example. The precordial electrode, placed over infarcted muscle, was negative ( $V_P$ ). The left leg ( $V_F$ ) also showed a negative potential, but the peak of its curve came very much

\*This patient came to necropsy three and one-half months after the curves shown in Fig. 6 were recorded. The heart weighed 700 gm. More than half of the anterior surface was made up of left ventricle. The parietal pericardium was adherent to the bulging anterolateral aspect of this chamber. There was extensive, old infarction of the entire left apex, the apical four-fifths of the anterior and lateral walls of the left ventricle, and the apical four-fifths of the anterior third of the interventricular septum. The endocardial surface of the infarcted area was covered with a thick, organizing mural thrombus.

There was marked atherosclerosis of the first 2.5 cm. of the anterior descending branch of the left coronary. The remaining lumen was occluded by an old, partially organized thrombus.

later than that of the precordial potential, indicating a different origin. This peak was simultaneous with, and therefore responsible for, the inverted deflection in the QRS complex of Lead V since there is only a suggestion of such a deflection in the precordial potential,  $V_P$ .

A striking experimental example of this can be seen in the article by Wilson and his associates<sup>15</sup> on myocardial infarction produced in dogs by ligation of the septal branch of the left coronary artery. In *Fig. 4*, on page 601 of that article, the potential variations of the left hind leg are very much larger than those of several precordial points. The effects of pairing each of the precordial points with the left hind leg are shown in *Fig. 5* on the next page. The curves thus obtained are decidedly dominated by the potential variations of the left hind leg, and are very different from those representing the true precordial potentials.

A clinical example of a precordial electrocardiogram dominated by potential variations of the distant electrode was not seen in this small series, and it would seem unlikely that such an extreme situation ever exists in humans. However, the many curves thus far published, showing marked differences between Leads IV and V, are evidences of the extent to which potential variations of the distant electrode may distort the precordial electrocardiogram.

In this group, Case 2, *Fig. 4*, is an example. Leads IV and V differ considerably from each other and from the true precordial potential,  $V_P$ . An important point is brought out by these electrocardiograms. The prominent notch on the descending limb of the QRS of  $V_P$  is almost absent in Lead IV. The reason for this is apparent if  $V_R$  is examined. The last QRS deflection in this curve is upward. With the comparator it was discovered that this was simultaneous with the notch seen in  $V_P$ . Since both are approximately the same size, and since both represent simultaneous negative variations in potential of the two points concerned, then when the difference in potential between these was taken (Lead IV), the notch practically disappeared. The reverse occurred in one instance (Case 1). Both slurring and notching in Lead V were due to potential variations of the left leg, rather than of the precordium.

#### SUMMARY AND CONCLUSIONS

The qualitative and quantitative effects of the potential variations of the distant electrode in Leads IV and V of Wolfarth and his associates have been demonstrated with the aid of an indifferent electrode shown by Wilson and his coworkers to be at zero potential throughout the cardiac cycle. The potential variations of the left leg, or of a point on the back, medial to, and just below, the inferior angle of the left scapula, were usually small compared with the potential variations

of the precordium. In the cases studied, the latter dominated the form of the electrocardiogram obtained when the precordium was paired with either the point on the back or the left leg, as in Leads IV and V.

The time of the "intrinsic deflection," when this could be identified, was usually the same in Lead IV, Lead V, and in the curve representing the potential of the precordium. Slurring and notching in electrocardiograms obtained by leading from two points on the body may be due to potential variations of the distant electrode. If the position and size of the exploring electrode are kept constant, marked differences between Leads IV and V can be due only to considerable differences between the potential variations of the back and the potential variations of the left leg.

#### REFERENCES

1. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
2. Wilson, F. N., Macleod, A. G., Barker, P. S., and Klostermeyer, L. L.: Electrocardiogram in Myocardial Infarction With Particular Reference to Initial Deflections of Ventricular Complex, *Heart* 16: 155, 1933.
3. Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *AM. HEART J.* 9: 459, 1934.
4. Wilson, F. N., Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *AM. HEART J.* 9: 472, 1934.
5. Kossmann, C. E., and Johnston, F. D.: The Precordial Electrocardiogram: I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 10: 925, 1935.
6. Wood, F. C., Bellet, S., McMillan, I. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
7. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Accuracy of Einthoven's Equation, *AM. HEART J.* 7: 203, 1931.
8. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, University of Michigan Studies, Scientific Series, Vol. X, University of Michigan, 1933.
9. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1930.
10. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Onset of Ventricular Excitation in Human Bundle-Branch Block, *AM. HEART J.* 7: 305, 1932.
11. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart, Part II: The Ventricle, *Phil. Tr. Roy. Soc. (London)*, B. 206: 181, 1915.
12. Barker, P. S., Macleod, A. G., Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, *AM. HEART J.* 5: 720, 1930.
13. Wilson, F. N., Johnston, F. D., Hill, I. G. W., and Grout, G. C.: The Electrocardiogram in the Late Stages of Experimental Myocardial Infarction, *Tr. A. Am. Physicians* 48: 154, 1933.
14. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart Beat at the Apices of Einthoven's Triangle, *AM. HEART J.* 7: 207, 1931.
15. Wilson, F. N., Hill, I. G. W., Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: I. Septal Infarcts and the Origin of the Preliminary Deflections of the Canine Levocardium, *AM. HEART J.* 9: 596, 1934.
16. Wood, F. C., and Wolferth, C. C.: Huge T-Waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9: 706, 1934.
17. Bobb, L. R.: On the Use of Chest Leads in Clinical Electrocardiography, *AM. HEART J.* 10: 728, 1935.

## HEMICONSTRICTION OF THE VASCULAR SYSTEM ASSOCIATED WITH CEREBRAL DISEASE\*

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IT IS generally recognized that patients with hemiplegia may exhibit changes in temperature, color, and sweating of the paralyzed extremities and that edema of the involved limbs may be present. Within the past few years there has been renewed interest in these phenomena, especially in view of the work of J. F. Fulton and his associates,<sup>1</sup> who have observed and studied vasomotor effects of central origin, in the course of their investigation concerning the functions of the premotor area of the cortex. Following ablation of this area in monkeys, they have consistently observed vasomotor phenomena in the contralateral extremities, and they consider these autonomic effects to constitute one of the characteristics of the "syndrome of the premotor area." Both experimentally and clinically, however, it is extremely rare in hemiplegic limbs to find a marked diminution in the blood pressure and in the pulsations of the major arteries of the affected side. During the past two years we have been fortunate in being able to study a patient who has a remarkable hemiconstriction of the vascular system associated with cerebral disease of the opposite hemisphere.

### CASE REPORT

H. M., a thirty-three-year-old American clerk, entered the University of California Hospital for the first time in April, 1934, with the chief complaint of convulsive seizures of nine years' duration. He had been well until the age of twenty-three, ten years before entry. At that time he developed an infected right lower molar tooth. A week prior to the extraction of the tooth he complained of a very severe frontal headache lasting for one day. Following the extraction, he partook of considerable alcohol, and two days later after drinking excessively at a party he became unconscious, but awakened the following morning feeling well and remained so until noon when he again fainted while at work. During the ensuing week he felt well, then he awakened one morning feeling confused and drowsy and was unable to speak. This motor aphasia persisted, and two days later he was transferred to the Methodist Hospital in Omaha, Neb. Two days after arriving there, he first noticed that the right side of his face, his right arm, and right leg were paralyzed. A letter from the Methodist Hospital informs us that he had a very typical motor aphasia with the usual findings of right hemiplegia. His temperature was normal, and his pulse varied between 55 and 60. His spinal fluid pressure was slightly over 200 mm. of water, and there were 25 cells per cubic millimeter, 92 per cent of which were lymphocytes. The Lange curve was 3345410000, and the blood and spinal fluid Wassermann tests were negative. It was the impression of Dr. G. Alexander Young

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that the patient's lesion was in the left lower central parietal region, and the pathological process was considered to be one of three: a focal encephalitis, a cerebral abscess or a tumor. After eight weeks in the hospital his speech and muscle power had begun to return. He noticed at this time that his right side was cooler

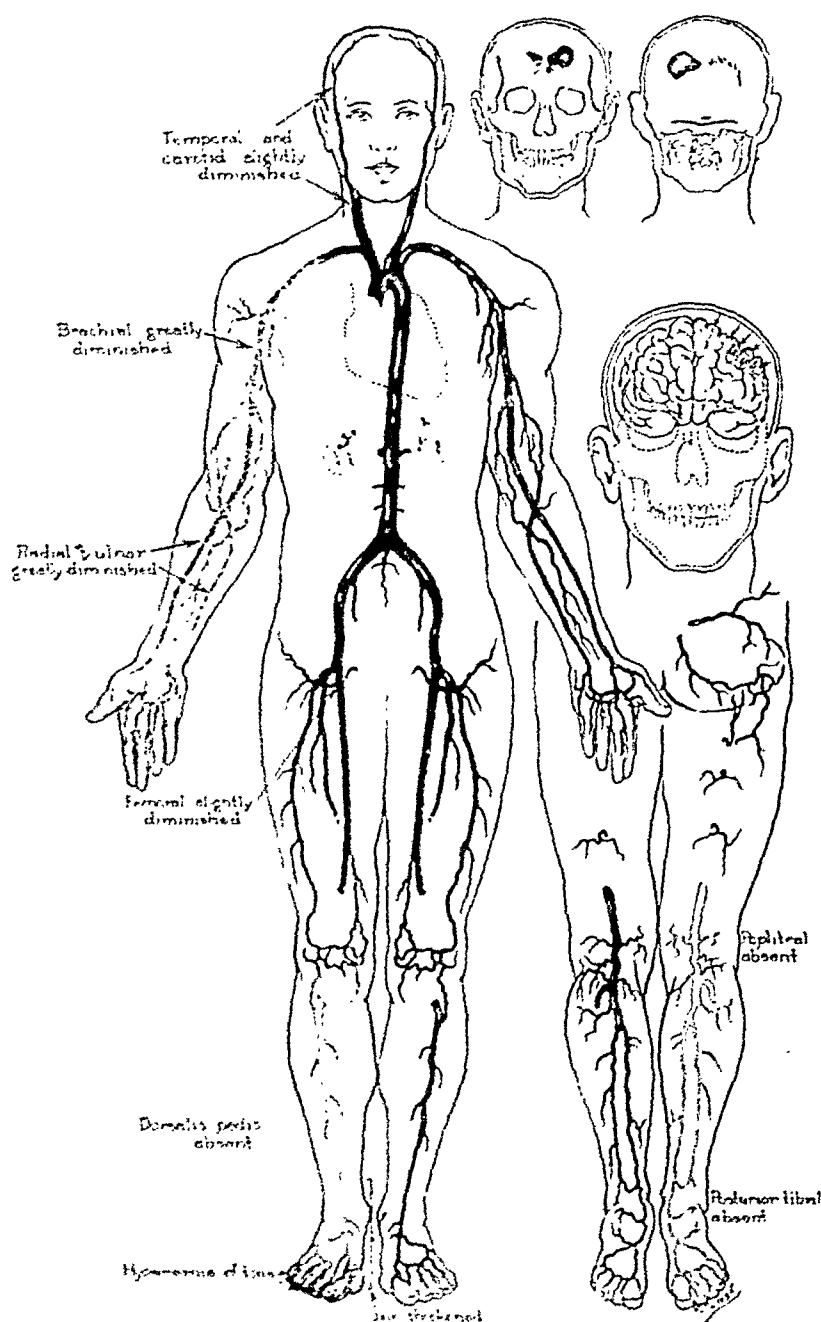


FIG. 1.—Illustrating the unilateral vasoconstriction, and the region of the brain affected.

and perspired less than his left. Also he observed that the pulse at his right wrist was weak, and at times could not be felt. One year after discharge from the hospital there was little residual paralysis, and speech had returned fairly well. At this time he had a short "fainting spell" on one occasion, and several weeks later he had his first Jacksonian seizure, initiated by involuntary contraction of his right arm,

and rotation of the head to the right, followed immediately by unconsciousness and convulsions. After this time he had several seizures a year, and on one occasion in 1928 he had a series of fifteen successive convulsive attacks. Between 1928 and 1934 he had only two seizures, the last occurring two weeks before entry. All of the seizures have been similar, beginning with forcible raising of his right arm, and with sudden rotation of the head to the right, followed by unconsciousness and convulsions lasting for several minutes, and associated with the biting of his tongue

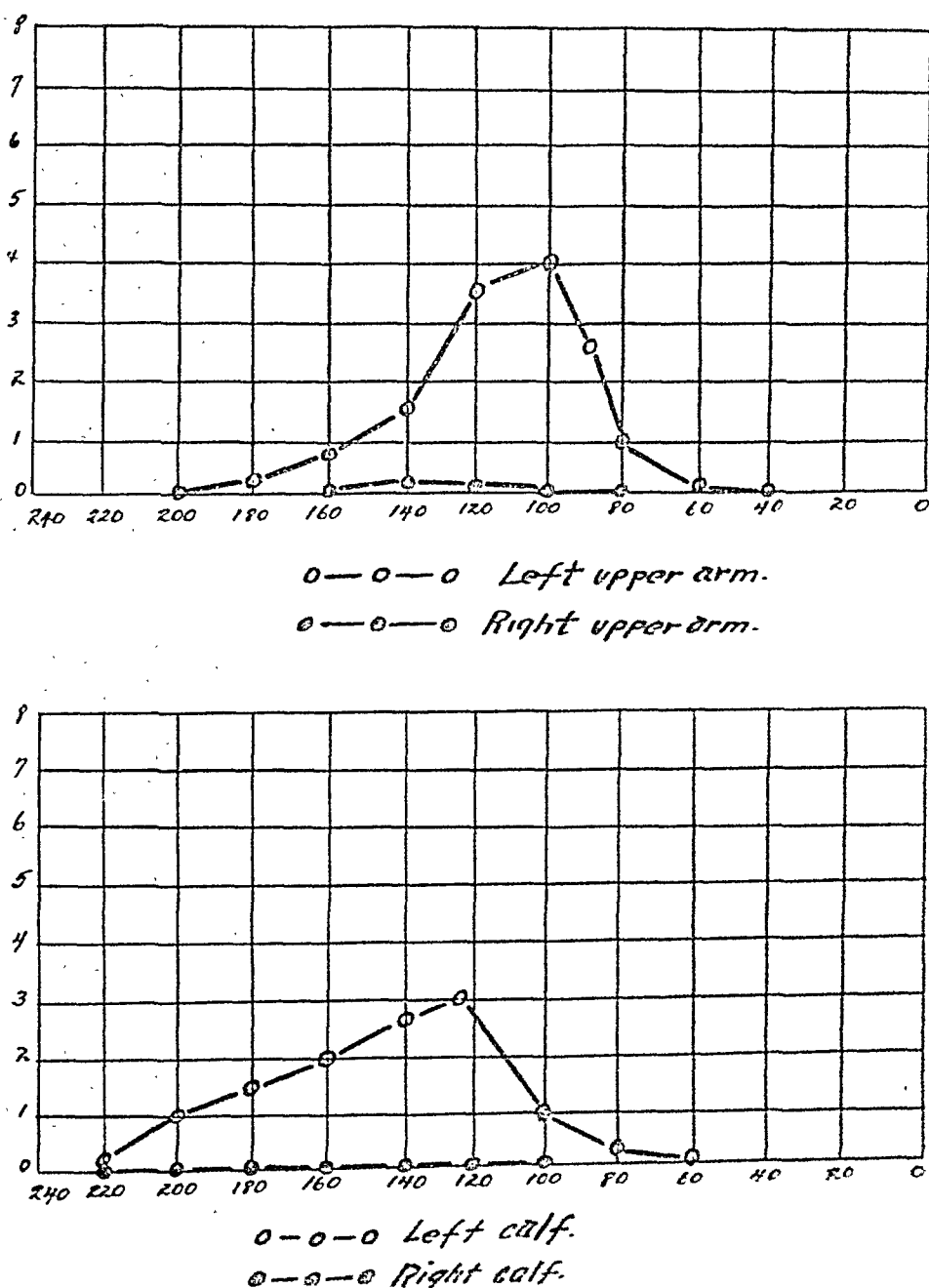


Fig. 2.—Oscillometry, showing no oscillations in the right extremities.

but without loss of sphincter control. During this entire time the patient's radial pulse on the right side has remained feeble or absent. There has been some variation in amplitude observed by him. At times the pulsation may be easily felt, but it has never been equal to the left radial pulse. He has had mild intermittent claudication in the right leg, and there has been slight edema of the ankle. He observed that his entire right side was cooler, and that it perspired less freely than the left side.

On physical examination in 1934 it was noted that he had a slight slurring and difficulty in speech, although the action of his palate and his tongue was normal.



The right facial muscles were definitely weak. The motor power of all extremities was good but was slightly less on the right than on the left, and the movements of the right arm and leg were noticeably clumsy. There was moderate atrophy and spasticity of the right limbs, and their reflexes were hyperactive. He had a sustained ankle clonus and Babinski sign on the right. The most striking finding on physical examination was that the radial and brachial pulsations were barely perceptible on the right side, and the popliteal, dorsalis pedis, and posterior tibial arteries could not be felt to pulsate on that side. The pulsations of the temporal, carotid, and femoral arteries were found to be very slightly diminished on the affected side (Fig. 1).

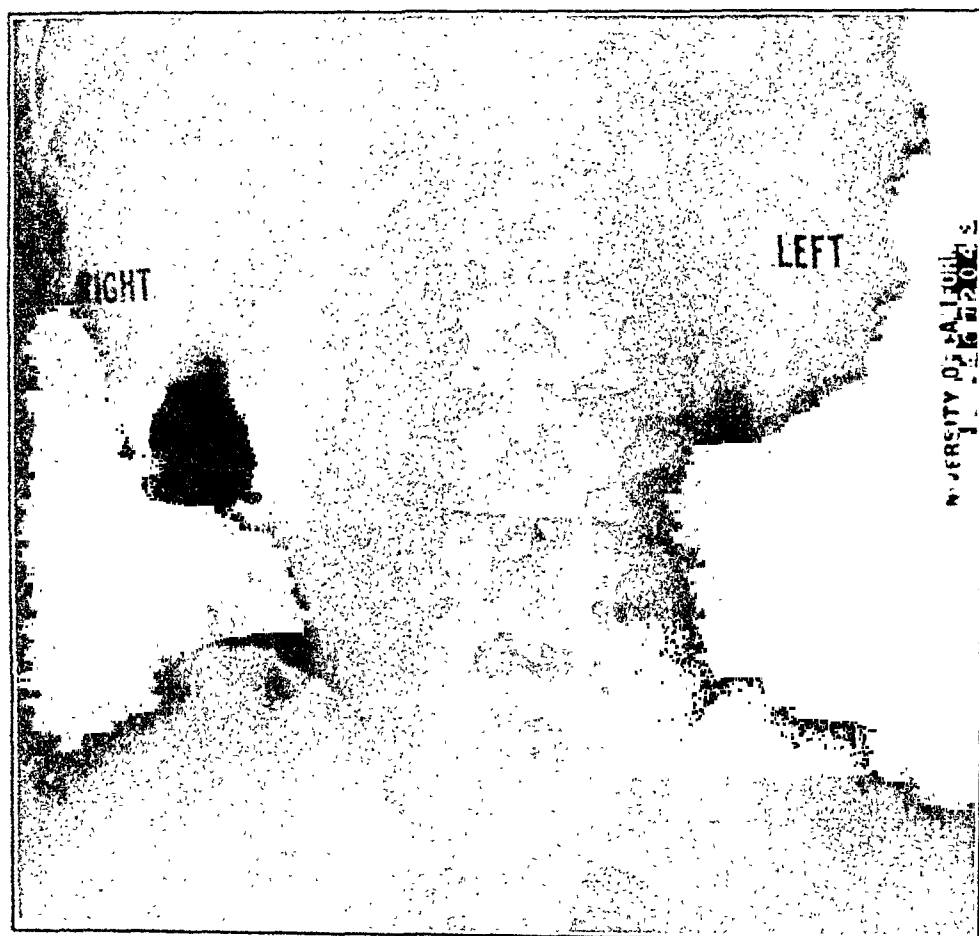


FIG. 2.—Intravenous pyelograms, showing right pelvis and calyces reduced in size as compared with those of the left kidney.

There appeared to be no difference in the retinal arterioles of the two sides. The blood pressure could not be obtained in the right arm and leg by the usual method. The skin of the extremities on the affected side was slightly cooler and drier than that of the normal side, and there was the peculiar thickening and hypertonus of the skin on the right side that one of us (Wm. J. K.) has frequently observed with lesions of the spinal cord; this effect presumably resulting from interference with the autonomic fibers supplying the skin.\* There was slight edema of the right ankle, and, when the leg was held in a dependent position, there was considerable cyanosis of the toes. The pulsations of the major arteries on the left side were all of

\*This will be the subject of a report by Wm. J. Kerr, M.D., and Charles A. Noble, Jr., M.D.

good amplitude; however the vessels were distinctly thickened and tortuous; and the blood pressure was elevated (180/110 left arm, and 210/120, left leg).

*Course.*—Since the patient's first admission in 1934 there has been essentially no change in his neurological status. He has had three jacksonian seizures, the last occurring in March of this year. It is of interest that toward the end of this last convulsion, and for at least twenty minutes thereafter, his wife observed that his pulse at the right wrist was much more easily felt than usual, although it was still not equal in amplitude to that of the left. Other than for this observation there has been no noticeable change in arterial pulsations; however, there has been considerable change in the appearance of the right foot. Whereas in 1934 the patient's chief complaint was the convulsive state, now it is related to the disability from his right lower extremity. When he hangs his foot in a dependent position there now occurs

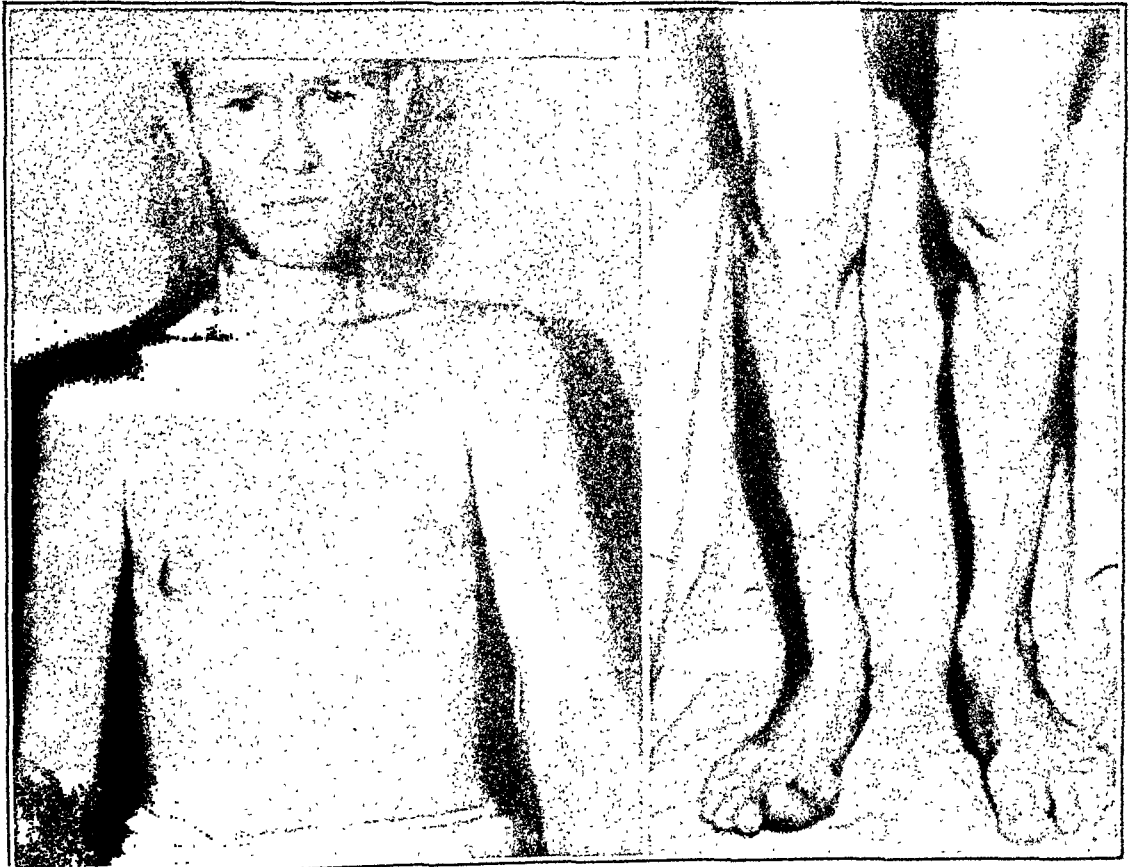


Fig. 4.—Infra-red photographs, showing the increased venous markings on the right side, as compared with those on the left. The hyperemia of the toes and glossy appearance of the skin are also illustrated.

a remarkable reddish blue hyperemia of the toes, similar to that seen in thromboangiitis obliterans. The toenails of the right foot have become thickened and brittle. The skin of the foot is thickened and glossy, and on one occasion he developed small patches of scleroderma on the ankle and calf. On numerous occasions he has had thrombophlebitis of some of the smaller veins in the right lower leg. Eight months ago he first noticed a callus on the ball of his right foot. This became infected and was drained, but it failed to heal properly and still caused him considerable discomfort. As before, we are unable to obtain his blood pressure by the usual method; however, by the "two cuff" method it has been determined to be 118 mm. systolic in the right arm as compared to 160 in the left arm, and only 50 in the right leg as compared to 196 in the left leg. By osillometry there were found to be no oscillations in the right extremities, whereas in the left extremities the curve was essentially normal (Fig. 2).

*Laboratory Data and Special Procedures (Table I).*—The fact that nearly all of the major vessels of the right side are affected to some degree is, in itself, good evidence against there being any extrinsic peripheral mechanism responsible for the vascular changes; however, by means of x-ray films of the cervical spine we excluded cervical rib. A film of the chest showed normal heart and lungs, and no evidence of anomalous vessels. Films of both arms showed no evidence of calcification in the arteries, and the bones appeared normal. It is of interest that intravenous pyelograms showed a small right kidney with pelvis and calyces reduced in size as compared with the left kidney (Fig. 3).

Our second group of studies was concerned with vasomotor phenomena. Skin temperatures were slightly lower on the right than on the left side, and the rise with spinal anesthesia was not quite as great in the right leg as in the left. The pulsations of the vessels still could not be felt after spinal anesthesia. There was, likewise, no increase of pulsations on the right side during deep anesthesia with ether. Exercise, immersion of the extremities in warm water, and inhalation of amyl nitrite made no appreciable difference in arterial pulsations. Assuming that the increased pulsations noted during his last convulsion might be due to increased blood pressure, we attempted to reproduce this condition by giving the patient 1 c.c. of 1:1,000 adrenalin (intramuscularly), and somewhat to our surprise we found that, although there was the usual marked rise in the left extremities, there was no appreciable change in the blood pressure of the right arm and leg. Pilocarpine (10 mg.) seemed to increase slightly the pulsations in the right radial artery. The sweating induced by this drug was approximately equal on the two sides. The histamine flare test was equal and normal on the two sides. Infra-red photographs of the trunk and extremities showed an increased venous circulatory bed on the right side as compared with the left (Fig. 4). Arteriograms were attempted but were

TABLE I  
SUMMARY OF DATA COMPARING LEFT AND RIGHT EXTREMITIES

RIGHT	DIAGNOSTIC PROCEDURES	LEFT
Arm ----- 118 mm.	Blood pressure (two-cuff method).	Arm ----- 158 mm.
Leg ----- 99 mm.		Leg ----- 196 mm.
No oscillations.	Oscillometry.	Normal.
Pelvis and calyces reduced in size.	Renal function as suggested by intravenous pyelograms.	Pelvis and calyces approximately normal.
Slightly cooler than left (av. 1.2°).	Skin temperature.	Normal.
Slightly less of a rise than on left. No change in arterial pulsations.	Skin temperature after spinal anesthesia.	Normal rise.
No change in arterial pulsations.	Exercise. Inhalation of amyl nitrite. Immersion of extremity in warm water.	Normal response.
Marked sweating. Slight increase in amplitude of radial pulse.	Pilocarpine, 10 mg. (s.c.).	Marked sweating.
No rise in blood pressure.	Adrenalin, 1:1,000, 1 c.c. (s.c.).	Marked rise in blood pressure.
Normal response.	Histamine flare.	Normal response.
Thickening of dermis. Thrombophlebitis of several small veins.	Biopsy of skin (lower legs).	Normal.
Normal arterioles.	Biopsy of pectoral muscles.	Normal arterioles.

unsuccessful because of the difficulty in introducing a needle in the right femoral artery. Biopsy of the skin from the right ankle showed moderate thickening of the skin, and a small thrombosed vein with the lumen full of leucocytes, red blood cells, and fibrin. Biopsy of the pectoral muscles on both sides showed normal appearing arterioles.

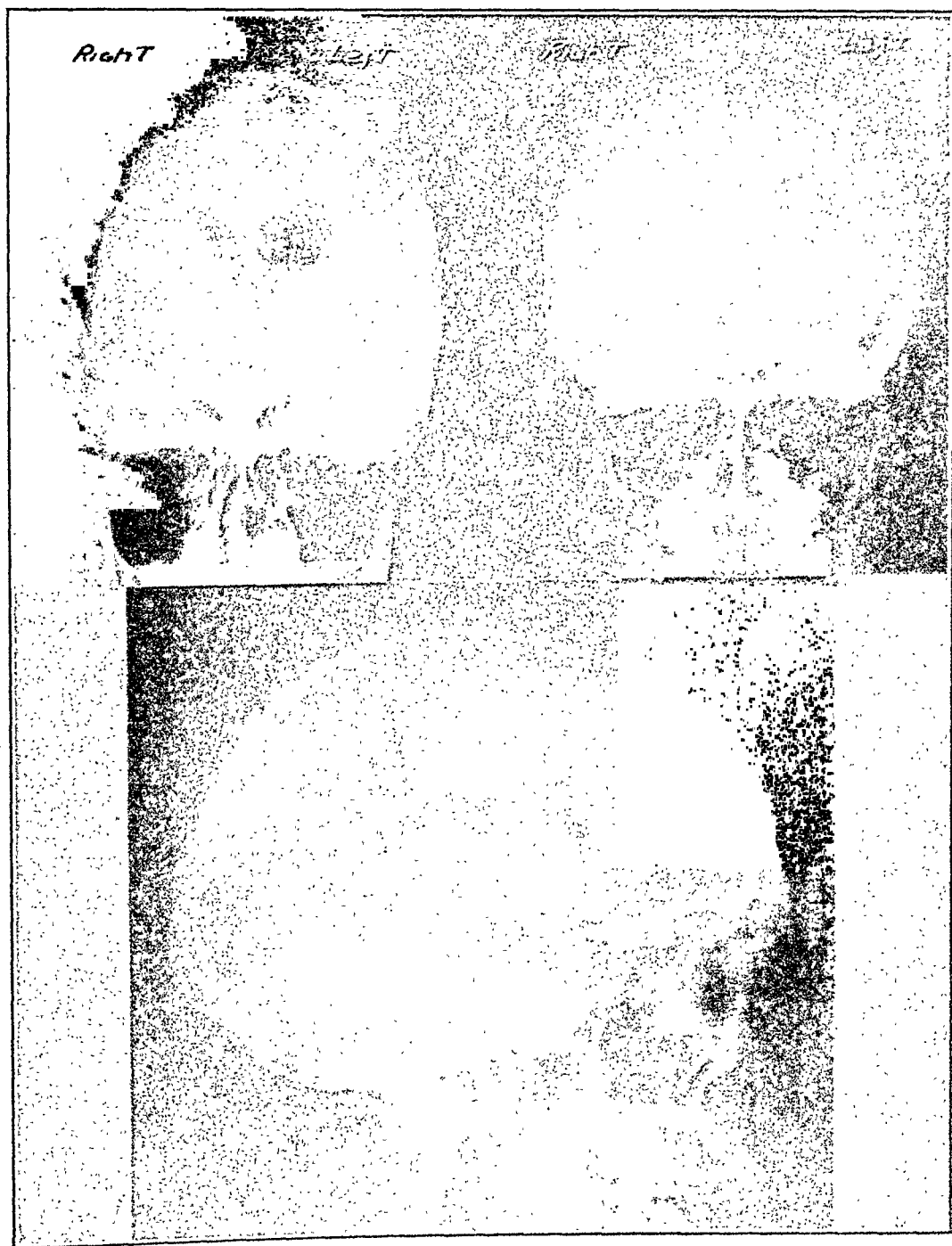


Fig. 5.—Encephalograms showing the dilated left ventricle (anterior and posterior horns), and the displacement of the third ventricle to the left. The films also show air distributed over the left cortex in dilated sulci, indicating cortical atrophy.

A third group of studies has been made to determine if possible the nature of the central lesion. X-ray films of the skull, visual fields, and spinal fluid were all normal. Encephalograms show "a unilateral dilatation of the left ventricle involving all portions of the ventricles, and the third ventricle is displaced about 4 mm. to the left of the midline. In addition, there is a large amount of air which has reached the subarachnoid space over the cerebral cortex on the left side and is distributed in

dilated sulci, which is evidence of a high degree of cortical atrophy. This is most marked in the posterior portion of the frontal lobe, and in the temporal and parietal lobes. The outlines of the right ventricle appear normal" (Fig. 5).

#### DISCUSSION AND CONCLUSIONS

The etiology of this patient's cerebral lesion is not entirely clear. Cerebral thrombosis would seem to be the most plausible diagnosis. However, we assume that he has a high degree of atrophy and scarring of the left cortex. There is evidence of only minimal impairment of motor power in the right extremities, whereas the vascular changes are remarkable. In view of the work of Fulton and his coworkers, who have shown that in hemiplegia the spasticity, impairment of coordinated movements, and vasomotor phenomena are characteristic of lesions involving the premotor area, one may perhaps attribute some of the findings in our patient to involvement of the left premotor area. In this regard it is of some interest that his Jacksonian seizures begin with complex involuntary movements of the arm and head, and that, according to Fulton and Viets, this type of reaction is more typical of premotor seizures than of those arising in the motor area, in which case the seizures are more likely to begin in one muscle group and to progress in characteristic manner to other larger muscle groups.

In considering the vascular changes which this patient shows in his right extremities, we find that they are out of proportion to the muscular spasticity and weakness, and therefore cannot be attributed to atrophy and disuse of the extremities. The history suggests that there may be some degree of spasm of the arteries on the right side, inasmuch as the patient has noticed some variation in the amplitude of pulsations of his right radial artery. Also in favor of this view is the fact that pulsations were noticeably greater following an epileptic seizure; however our vascular studies indicate no evidence of spasm. In the right leg, especially, the patient now demonstrates nearly all of the findings associated with occlusive disease affecting the larger vessels, and the listing of these findings would read almost like a textbook description of thromboangiitis obliterans; namely, absent pulsations, intermittent claudication, hyperemia in dependent position, delayed reactive hyperemia, trophic changes in the skin and nails, and recurrent phlebitis. Inasmuch as the change in the arterial pulsations was observed so soon after the patient's hemiplegia, it seems quite possible that vasospasm may have been predominant for a time following the hemiplegia or may possibly have preceded it, but now there is evidence of organic occlusive arterial disease which has progressed considerably during the two years while we have observed him. He undoubtedly has developed a fairly extensive collateral circulation, and we see evidence of this in the infra-red photographs.

In the literature there are many observations concerning the blood pressure in hemiplegic patients. These have been ably reviewed in a

recent article by P. C. Bucy,<sup>2</sup> who found that there was a great discrepancy in the findings of various observers. The blood pressure on the paralyzed side has been reported to be higher than on the normal side in some patients, and lower in others. He states that the reported findings are hard to evaluate because of the fact that normally there may be considerable difference in the blood pressures on the two sides. More consistent observations have been made concerning temperature changes, and it is fairly well established that early in the course of a hemiplegia the affected side is likely to be warmer, and later to become colder than the normal side. Bucy has reported a patient who developed a sudden right hemiplegia eight days following an automobile accident. The right arm was cold and cyanotic, and the pulse and blood pressure could not be obtained. However, over a period of days the pulse and blood pressure gradually returned to normal. In reviewing the literature he was able to find a report of only one patient with an old hemiplegia, in whom the blood pressure could not be obtained on the paralyzed side.<sup>3</sup>

Penfield<sup>4</sup> in 1933 reported thirty patients with epilepsy in whom he induced attacks by stimulating the cortex directly. Accompanying these seizures, there were interesting vasomotor phenomena occurring in the vessels of the brain, namely, arrest of visible pulsations in the arteries and engorgement of veins. Usually this vasoconstriction was quite widespread, although occasionally the arterial pulsations disappeared in a localized area, and immediately after the convulsion transient focal areas of cortical anemia could be seen. Following the seizures, the arteries pulsated violently and became bright red. Penfield observed on several occasions that with the central arterial spasm the radial pulse also disappeared completely for a short period.

Zenner and Kramer<sup>5</sup> have reported a patient in whom the right radial pulse could not be felt during the removal of a dural endothelioma from the left side. Osler,<sup>6</sup> in an article published in 1896 entitled "The Cerebral Complications of Raynaud's Disease," described a patient with aphasia and a right hemiplegia who had local asphyxia of the right hand and finally gangrene of the fingers. These and other reports suggest that a high degree of peripheral vasoconstriction may be associated with cerebral disease.

In a study of vasomotor disturbances resulting from cortical lesions, Kennard<sup>7</sup> has shown that after ablation of the premotor area in monkeys and chimpanzees, the skin temperature of the contralateral foot was considerably lower than that of the normal side. She made the interesting observation that if the environmental temperature was low this difference was marked, but if it was relatively high there was very little, if any, difference in skin temperatures of the two sides. She found that the vasoconstriction was prompt and equal in both feet when an operated animal was placed in a cold environment, but when it was then rapidly transferred to a warm environment there was a distinct lag in vasodilata-

tion on the affected side, thus indicating an impairment of the vasodilator mechanism resulting from ablation of the premotor cortex. Other autonomic effects observed were transient edema, changes in the color of the skin, and diminished perspiration on the affected side. No change in blood pressure was observed.

The corticospinal pathways from the premotor area have not yet been completely traced; however, the course of these fibers has been clarified considerably by the recent investigations of Hoff<sup>8</sup> and of Kennard.<sup>9</sup> Very little is known about the corresponding corticospinal autonomic pathways. They probably traverse the capsule in company with the pyramidal fibers. Hunsicker and Spiegel<sup>10</sup> have produced changes in skin temperature of the contralateral extremities by cortical stimulation in cats, and this effect persists after section of either the pyramidal or the extrapyramidal projection systems but disappears when both tracts are cut, indicating probably more than one pathway for vasomotor fibers. It is known, of course, that there are vasomotor centers in the hypothalamus, and it has been suggested that these are under the inhibitory control of the cortex. With destruction of the cortex, according to this hypothesis, these lower centers are "released" to increased activity, thus giving rise to vasomotor effects. As Kennard points out, it is impossible to say whether some of the effects are due to cutting off of an active vasodilator mechanism, or to the removal of an inhibitory effect on the mechanism of vasoconstriction.

Summarizing the sequence of vascular changes in our patient, we presumed that vasoconstriction of the larger vessels of his right extremity occurred following the cerebral accident. At least we can say that there was probably interference with the autonomic nerve supply to the skin and blood vessels, and that this presumably resulted from involvement of the premotor area of the left cortex.<sup>6</sup> Structural changes have now occurred in the larger arteries of the right side. Possibly the profound vasomotor imbalance incident to his hemiplegia hastened the evolution of an occlusive arterial disease. We know that even the vessels of his left side are abnormally thickened and tortuous and that he has hypertension on that side. Considering the frequency of hemiplegia and the rarity of such marked and persistent changes in pulse and blood pressure, one must probably assume some such unknown factor. Whatever the mechanism, there is evidence that the patient now has unilateral obliterative arterial disease, which simulates thromboangiitis obliterans in many respects.<sup>7</sup>

<sup>6</sup>Fulton and Kennard have reviewed the data presented and suggest that one cannot exclude other cortical areas or the subcortical nuclei from consideration in this case. Likewise, we have no proof that hemivascular constriction preceded the attack of hemiplegia. Under the circumstances the unilateral changes cannot be attributed to a premotor lesion alone.

<sup>7</sup>During the past week we have observed four patients with premotor lesions on the non-dominant side of Dr. H. C. Naffziger. Each of these patients had been treated upon a convulsive basis with tumors in the right hemisphere and two with traumatic lesions in the left hemisphere. In only one were there any significant structural changes; in this case, a young man who had suffered from a hemorrhage in the left premotor area, after being struck by a baseball and the clot evacuated, showed two weeks later greater pulsations in the vessels and some relaxation of the skin on the right (opposite) side.

## SUMMARY

The case report is presented of a male, aged thirty-four years, who was found to have marked vasoconstriction of the major arteries of his right extremities, following a right hemiplegia in 1924. Jacksonian epileptic seizures beginning in the right arm likewise ensued following the cerebral accident.

Prominent findings at present are: (1) the absence of pulsations in the larger arteries of the right side, with other evidence of vascular insufficiency; (2) the finding of hypertension on the opposite (left) side; (3) encephalographic evidence of marked atrophy of the left cerebral cortex. Vascular studies indicate that vasospasm is minimal or absent, and there is evidence of unilateral obliterative arterial disease. In view of the recent observations of J. F. Fulton and his associates, it is suggested that vasomotor effects of central origin may have preceded and precipitated these changes.

## REFERENCES

1. (a) Fulton, J. F., Jacobsen, C. F., and Kennard, M. A.: A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys, *Brain* 55: 524, 1932.
- (b) Fulton, J. F.: Paralysis of Cortical Origin, *Proc. Calif. Acad. Med.*, pp. 1-20, 1933, 1934.
- (c) Kennard, M. A., and Fulton, J. F.: Localizing Significance of Spasticity, Reflex Grasping, and the Signs of Babinski and Rossolino, *Brain* 56: 213, 1933.
- (d) Fulton, J. F.: Forced Grasping and Groping in Relation to the Syndrome of the Premotor Area, *Arch. Neurol. & Psychiat.* 31: 221, 1934.
- (e) Kennard, M. A., Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man; Impairment of Skilled Movements, Forced Grasping and Vasomotor Disturbance, *Brain* 57: 69, 1934.
- (f) Fulton, J. F., and Viets, H. R.: Upper Motor Neurone Lesions: An Analysis of the Syndrome of the Motor and Premotor Areas, *J. A. M. A.* 104: 357, 1935.
2. Bucy, P. G.: Vasomotor Changes Associated With Paralysis of Cerebral Origin, *Arch. Neurol. & Psychiat.* 33: 30, 1935.
3. Melchior, E., and Wilimowski, M.: Ueber das Verhalten des Pulses in gelähmten Gliedmaßen, *Zentralbl. f. Chir.* 43: 49, 1916.
4. Penfield, W.: The Evidence for a Cerebral Vascular Mechanism in Epilepsy, *Ann. Int. Med.* 7: 303, 1933-34.
5. Zenner, P., and Kramer, S. P.: Operation for Brain Tumor With the Occurrence of Hitherto Unrecognized Circulatory Phenomena, *New York M. J.* 90: 651, 1909.
6. Osler, Wm.: The Cerebral Complications of Raynaud's Disease, *Am. J. M. Sc.* 112: 522, 1896.
7. Kennard, M. A.: Vasomotor Disturbances Resulting From Cortical Lesions, *Arch. Neurol. & Psychiat.* 33: 537, 1935.
8. Hoff, E. C.: Corticospinal Fibers Arising in the Premotor Area of the Monkey, *Arch. Neurol. & Psychiat.* 33: 687, 1935.
9. Kennard, M. A.: Corticospinal Fibers Arising in the Premotor Area of the Monkey, as Demonstrated by the Marchi Method, *Arch. Neurol. & Psychiat.* 33: 698, 1935.
10. Hunsicker, W. C., Jr., and Spiegel, E. A.: Conduction of Cortical Impulses to the Autonomic System, *Proc. Soc. Exper. Biol. & Med.* 31: 974, 1933-34.



# THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING CORONARY ARTERY LIGATION IN DOGS\*†

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THIS report concerns itself with the results of serial studies of the electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery in dogs. The series of experiments was designed primarily to correlate the various changes incident to coronary closure, viz., electrocardiographic, chemical, histologic, and surface thermometric changes. An opportunity was thus afforded of interpreting the electrocardiographic findings in the light of these other changes, as well as to study more specifically the disturbances of rhythm and the deviations of the various components of the electrocardiogram. In other articles,<sup>1, 2, 3, 4</sup> the chemical, histological, and surface thermometric changes are commented upon at length.

## METHODS

The method of exposure and of ligation of the coronary artery is outlined in detail in a previous paper.<sup>1</sup> The hearts were exposed by an incision through the left fourth interspace and the anterior descending branch of the left coronary artery with its accompanying veins ligated within 2 cm. of its origin, after which the pericardium and chest wall were tightly closed. Anesthesia was obtained by the intraperitoneal injection of a 10 per cent solution of amytal in dosage varying from 0.3 to 0.5 c.c. per kilogram of body weight. The dogs employed weighed from 15 to 20 kilograms. Electrocardiograms were taken before operation, at hourly intervals for the first twelve hours after ligation, again at twenty-four hours, at daily intervals for the next week, and at weekly intervals thereafter, until the dogs succumbed or were killed. Conventional limb leads were used in all instances. Immediately after the termination of the experiments, necropsies were performed. The hearts were examined grossly for changes in consistency and appearance of the myocardium, and the coronary arteries were injected with bismuth (method of Gross) as well as carefully explored to determine whether the vessels had been completely occluded by the ligatures. Blocks of tissue were taken from the normal and infarcted zones for histologic study. Satisfactory electrocardiograms were obtained in fifty dogs and serve as the basis for the results reported.

## HISTORICAL

Negativity of the T-wave in the electrocardiogram in association with experimental ligation of the coronary arteries in dogs was first described by Kahn<sup>5</sup> (1911). This was confirmed by Smith<sup>6, 7, 8</sup> (1918, 1920, 1923) in a careful serial electrocardiographic study of dogs following ligation of the coronary artery, and as another result of this

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investigation he described changes in the initial deflection and the S-T segment. From clinical studies Pardee<sup>9</sup> (1920) stressed the S-T segment changes and described the high or low take-off of the S-T segment as particularly significant in recognizing myocardial infarction. Later, the "cove-plane" type of T-wave so frequently observed in acute and recent myocardial infarction was described by Oppenheimer and Rothschild<sup>10</sup> (1924). Parkinson and Bedford<sup>11</sup> (1928) expressed the opinion that daily variations in the characteristics of the S-T segment and T-wave deflections are of greater significance than changes in these components at any isolated interval; thus emphasizing, as Smith did, the importance of serial electrocardiographic studies in order to observe successive changes that may occur.

With these facts established, the electrocardiographic evidence of myocardial infarction became generally accepted, and attention was directed to the possibility of localizing the site of the infarction by the electrocardiogram. Parkinson and Bedford,<sup>11</sup> Barnes and Whitten,<sup>12</sup> Barnes and Mann,<sup>13</sup> and Crawford and his associates<sup>14</sup> have concluded that lesions in similar sites produce essentially the same type of curve, lesions in the left apical region anteriorly giving rise to a  $T_1$  type of curve, whereas lesions at the posterior and basal parts of the heart give rise to a  $T_3$  type of curve. Some doubt has been entertained regarding the specificity of these curves in localizing lesions, particularly in passing from experimental results to clinical analogy. This discussion has to do with the controversy regarding which artery may be involved, a question which seems to have been settled satisfactorily by the work of Wolferth and his associates<sup>15, 16, 17, 18</sup> with the use of direct chest leads. Barnes and Whitten<sup>12</sup> suggest that the apparently contradictory results may be due to a difference between the coronary circulation of the dog and man. Further consideration must also be given to the variations in the distribution of the coronary arteries and their branches.

Electrocardiographic studies in conditions not associated with coronary artery occlusion, such as rheumatic fever, pneumonia, pericarditis with effusion,<sup>19-28</sup> clearly indicate that the T and R-T changes are not specific for coronary closure and may be encountered occasionally in other conditions. Barnes and Mann have reported experiments in which simple opening of the pericardium without other changes produced T and R-T changes similar in character to those seen after coronary artery ligation. The work of Feil, Katz, Moore, and Scott<sup>19</sup> emphasizes the importance of regarding these electrocardiographic changes as an indication of ischemia irrespective of the cause.

#### CONTROL STUDY

For purposes of comparison, electrocardiographic tracings were taken in each instance before the operation was begun, the animal being under full amytal anesthesia at the time. As a further control,

two dogs were subjected to every detail of the operative procedure except for the actual tying of the ligature.

The electrocardiograms taken before the operative procedures were instituted indicate clearly the extreme variability of the so-called

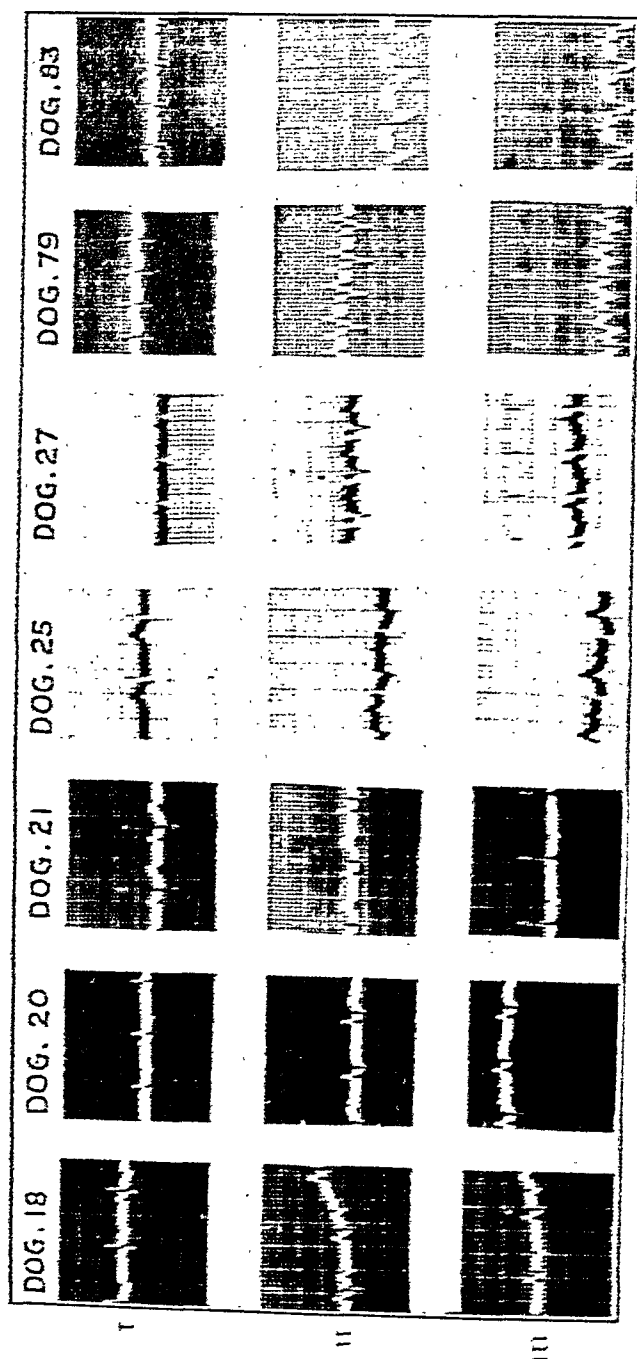


Fig. 1.—Control, variations in P-wave. Dog 28, inversion of P-wave in all leads, with cove-plane type of inversion in Lead III. Dog 29, denting of P-wave in Leads I and II, upright P in Lead III. Dog 26, upright P-wave in Leads I and II, inverted P in Lead III. Dog 25, flat P in Lead I, inverted, sharply pointed P in Lead II, upright P in Lead III. Dog 27, flat P in Lead I, diphasic P in Leads II and III. Dog 24, flat P in Lead I, deeply negative P in Leads II and III.

“normal tracing” of the dog (Fig. 1). Of the 50 dogs in which electrocardiographic data were available, T<sub>1</sub> was positive in 13 dogs, isoelectric in 10, diphasic in 2, and inverted in 25. The T negativity was of variable magnitude, usually sharply pointed, and not unlike that

described as "typical of coronary occlusion." Of the 25 dogs in which  $T_1$  was negative in the control period,  $T_2$  was positive in 6 instances, negative in 10, and diphasic in 9, while  $T_3$  was positive in 15 instances, diphasic in 4, and negative in 6. In only one instance was there any deviation of the S-T or RS-T segment of the electrocardiogram. In one of the two control animals no early electrocardiographic changes were noted. Nine hours after operation, however, there were slight directional changes in the T-waves, which became pronounced by the third, fourth, and fifth days, and were noted in lessened degree over a further period of three weeks. In the second control animal, slight S-T and RS-T changes were noted in the first nine hours postoperatively. Twenty-two hours after operation there were further directional changes in the T-waves, and two days later the dog was found dead.

#### COMMENT ON CONTROL STUDY

T-wave negativity, even of the cove-plane type in Lead I, Leads I and II, or in all three leads cannot be considered as pathognomonic of coronary occlusion. Moreover, it is evident that there is a marked variation in the normal tracing of the dog, and that the interpretation of any tracing after coronary closure is of no great value unless it is studied in comparison with a control tracing.

#### CHANGES FOLLOWING LIGATION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

The changes noted consisted chiefly of (a) disturbances of rhythm and (b) changes in the direction and configuration of various components of the electrocardiogram.

*Disturbances of Rhythm.*—Several types of arrhythmia were frequently encountered following coronary artery ligation. A large number of dogs (15 of 50) developed ventricular fibrillation either immediately or within ten minutes following ligation. Graphic tracings of several of these instances were recorded. When ventricular fibrillation did not occur immediately, there was usually a period of normal rhythm for a variable number of hours, following which in 18 recorded instances there appeared isolated premature ectopic contractions, arising as a rule from more than one focus, usually both nodal and ventricular, rarely auricular. These did not usually make their appearance before three hours after ligation—in some instances not before 24 hours after ligation. The greatest incidence of onset was from six to eight hours following ligation, 12 of the 18 appearing at this interval. In every instance in which ectopic beats appeared, a nodal or ectopic ventricular tachycardia followed within one to two hours. At first the intervals of tachycardia were brief, consisting of not more than 6 to 8 beats, but these quickly lengthened, and being a mixture

of tachycardias resulting from stimuli arising in different foci, the rhythm was grossly irregular. Those animals which developed ectopic

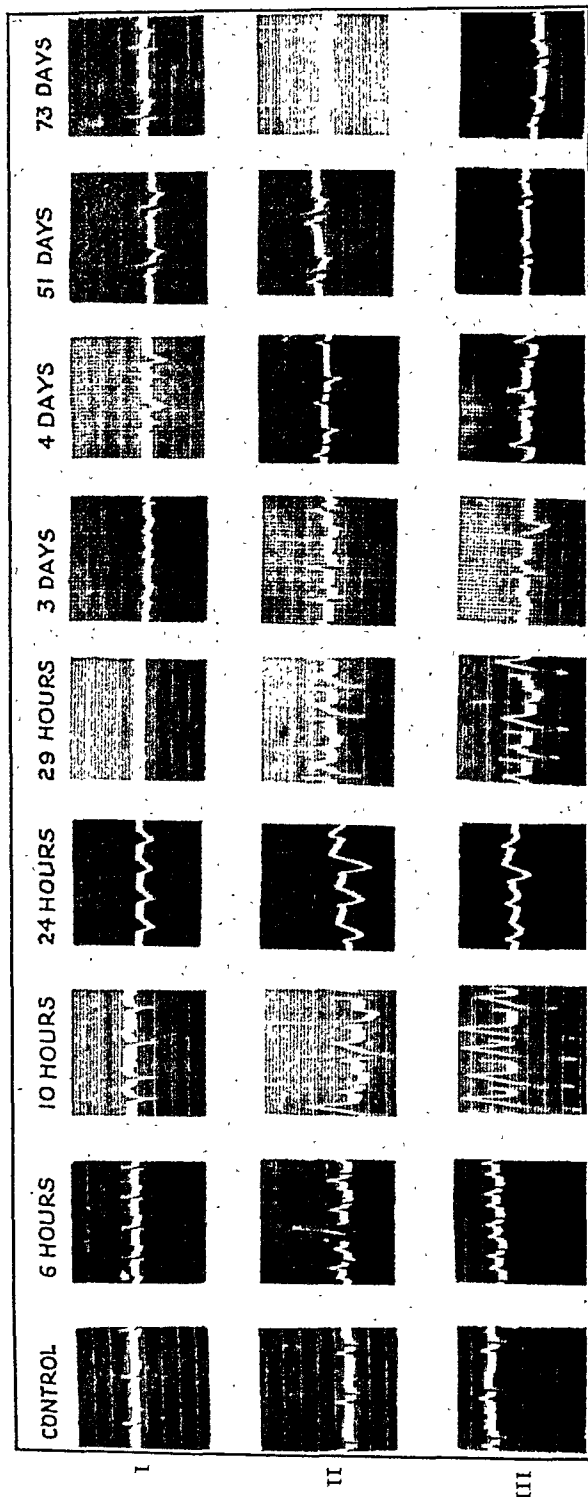


Fig. 2.—Disturbances of Rhythm—reversible sequence of rhythm changes. Isolated ventricular premature beat in Lead I, six hours following ligation. Mixture of premature beats and ectopic ventricular tachycardia ten hours after ligation. Impure ventricular flutter and ventricular tachycardia with questionable ventricular fibrillation in Leads II and III, 24 hours after ligation. Mixture of ventricular premature beats and ventricular tachycardia 29 hours after ligation. Isolated premature beats 3 days following ligation. Normal sinus mechanism 4, 51, and 73 days following ligation.

tachycardia were obviously in a terminal state, since they were found dead in their cages within twenty-four to forty-eight hours. It is quite likely that ventricular fibrillation followed these ectopic tachy-

cardias because it was possible to obtain a record showing the transition to ventricular fibrillation in several instances. In one instance the sequence of arrhythmia was reversible. There developed a sequence of premature beats, nodal and ectopic ventricular tachycardia, a brief

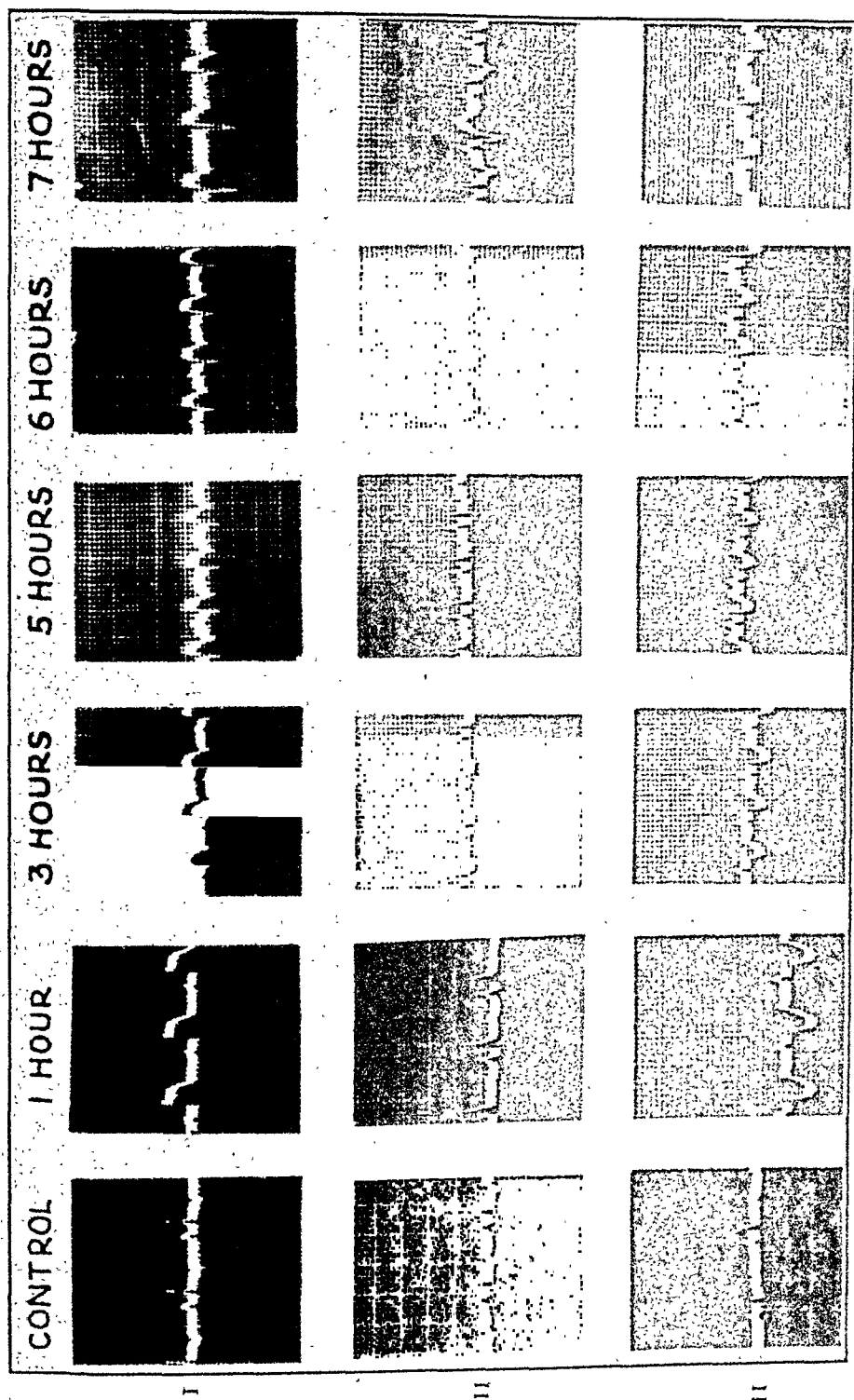


Fig. 3.—S-T Segment changes following ligation. Monophasic type of S-T wave in Leads I and III, 1 hour following ligation. Beginning of inversion of T in Lead I, appearance of negative T in Lead II and decrease of amplitude of S-T deviation in Lead III, 3 hours after ligation. High take-off in Lead I, and low take-off in Lead III, most conspicuous 1 hour after ligation, becoming progressively less prominent 3, 5, 6, and 7 hours after ligation. Typical cove-plane type of inversion of T in Lead I, 6 and 7 hours after ligation.

period of impure ventricular flutter, then ventricular tachycardia, nodal and ectopic ventricular premature beats, and finally normal rhythm (Fig. 2).

*Comment on Disturbances of Rhythm.*—The disturbances of rhythm incident to coronary closure are seen to follow a definite pattern.

Ventricular fibrillation is usually the terminal event in the series of rhythm changes. As a rule, the sequence of events is as follows: (1) premature beats arising singly and from various foci, usually ventricular and nodal, rarely auricular; (2) paroxysms of ectopic ventricular tachycardia, at first of short duration, later lengthening and followed by (3) ventricular flutter, usually very transient and passing almost immediately on to (4) ventricular fibrillation and death. The appearance, therefore, of isolated premature contractions following coronary artery closure is to be considered as having considerable prognostic import, presaging the possibility of the later occurrence of ectopic ventricular tachycardia, ventricular flutter, ventricular fibrillation, and death.

*Changes in Direction and Configuration of T, S-T and RS-T Components.—R-T Deviation* (Fig. 3): Within one hour following ligation, that is, in the acute stage of the myocardial damage, there was a deviation of the R-T or S-T segment from the isoelectric line. In Lead I in 26 of 33 dogs studied serially, the R-T segment of the curve started from the descending limb of the R-wave a variable distance above the isoelectric level. In 9 of these 26 instances the onset of origin of R-T above the isoelectric level was pronounced, varying from 3 to 6 mm., whereas in 17 instances this deviation was slight, varying from 1 to 3 mm. (1 mm. standardized to equal 1 mv.).

Where the high origin from the descending limb of the R-wave was pronounced (3 to 6 mm.) there tended to be a plateau-shaped, slightly convex elevation which then descended gradually to the isoelectric level at a point corresponding to what appeared to be the apex of a sharply pointed negative T-wave in subsequent curves. In those instances in which the origin above the isoelectric level was less pronounced (1 to 3 mm.), there was a very slight upward convexity which led immediately to a cove-plane, sharply pointed negative T-wave. In those instances in which the R-T<sub>1</sub> deviation was of great magnitude, the gradual descent to the isoelectric level and the apparent absence of the T-wave gave rise to a monophasic type of curve. This degree of elevation of the (R-T) segment above the isoelectric level appeared to be maximum in the first two hours after ligation, after which there was a gradual return to normal, requiring two to twenty-four hours for its completion. Definite T-waves in the monophasic type of curves were apparent before the R-T segment had completely returned to normal, and in every instance the direction of the T-wave was directly opposite to the deviation of the R-T segment. Where the R-T<sub>1</sub> deviation had been slight, the T-wave was negative in every instance. This corresponds to the T<sub>1</sub> type of curve described by Parkinson and Bedford<sup>11</sup> and by Barnes and Mann.<sup>13</sup>

In Leads II and III R-T deviations were also present, being particularly marked in Lead III, in which lead it was constantly opposite in

direction to that in Lead I. That is, where R-T arose above the isoelectric level in Lead I, there was a corresponding depression of R-T or (S-T) below the isoelectric level in Lead III. In the 7 instances in which R-T<sub>1</sub> deviations were not present, there was a noticeable depression of the R-T (S-T) level in Leads II and III, comparable, though in lesser degree, to that seen where R-T<sub>1</sub> changes were definitely present.

*T-Wave Changes.*—In the acute stage of the myocardial damage, as indicated above, the T-wave changes are essentially constant, being opposite in direction to the R-T or S-T deviation, and conforming to the T<sub>1</sub> type of Barnes and Mann<sup>13</sup> and of Parkinson and Bedford.<sup>11</sup> Essentially, they are inverted in Lead I and directed upward in Lead III. They tend, as a rule, to be sharply pointed, of the cove-plane type described by Oppenheimer and Pardee. Beginning about twenty-seven hours after ligation, the most conspicuous feature is the variability of the size, shape, and direction of the T-waves from day to day, following no fixed pattern, and showing changes over a period as long as seventy-three days. As a rule, the changes are in the direction of the normal, being first noticed in Leads II and III but often stopping short in Lead I so that T<sub>1</sub> may remain inverted or flattened. These facts indicate quite clearly that it is the change from day to day which is the feature of coronary closure rather than a characteristic coronary type of T-wave. Early there was frequently a conspicuous increase in the amplitude of the T-wave. As a rule, it required from one to four weeks before the T-waves assumed a normal appearance, but even after this period in some dogs T-wave changes persisted, particularly in Lead I and continued until the death of the animal.

#### OTHER ELECTROCARDIOGRAPHIC CHANGES

*QRS Waves.*—Contrary to clinical coronary occlusion, in which widening and notching of the initial ventricular deflection is commonly met with, this condition was rarely encountered in experimental occlusion in dogs. Low voltage of the QRS waves in Lead I was a noticeable feature in more than half of the experiments. It occurred either within the first three hours following infarction or not until about a week following the coronary occlusion. Rarely there occurred a subsequent increase in voltage, but as a rule, when once present, it persisted for the remainder of the experiment. It would seem, therefore, that a previous diffuse myocardial fibrosis is not necessary for low voltage of QRS and that coronary occlusion with myocardial infarction may, in itself, be sufficient to bring about this abnormality. Left or right axis deviation, bundle-branch block, accentuation of the Q-wave in Lead III were rarely encountered.



## EFFECTS OF RELEASE OF LIGATURE

In 8 dogs the coronary vessels were ligated for varying periods of time up to eight hours. At the end of different intervals the ligatures were removed and the animals killed two hours afterward. The most conspicuous result of releasing the ligature was the rapid onset of marked arrhythmia, premature beats, ventricular tachycardia, and in one instance ventricular fibrillation. It is interesting to note that, whereas no demonstrable characteristic alteration was observed in the myocardium of animals whose coronary vessels remained ligated for less than one hour, in this second group in which the ligature was released, striking gross and microscopic changes were present in every case except in one instance in which the vessels were ligated for only one-half hour.

## CORRELATIVE DISCUSSION

In correlating the electrocardiographic changes with the thermometric, anatomical, and chemical changes as reported in previous papers, several features are of interest. The immediate fall of surface temperature in the ischemic zone, the marked anatomical changes as indicated in these experiments in which the ligatures were released at varying periods up to eight hours after ligation, the immediate increase up to 100 to 200 per cent of lactic acid, with a similar decrease in glycogen content over that of the control zone—all these findings indicate a profound alteration in the ischemic zone. It is not at all surprising, then, that this injured zone profoundly and regularly alters the normal action current of the heart in a conspicuous and characteristic fashion, immediately after coronary closure.

## GENERAL DISCUSSION

It is apparent that in dogs there is a marked normal variability of the T-waves,  $T_1$  negativity being chiefly encountered, but negativity of T being found also in Leads II and III. It is further apparent that the so-called characteristic coronary type of T-wave (Pardee) or cove-plane type of T-wave (Oppenheimer) may also be encountered during experimental procedures in dogs in the absence of coronary ligation and with no evident myocardial injury. Deductions derived from the appearance of the T-waves of dogs are therefore of little value unless control tracings are available for comparison.

From the experimental results presented, it would appear that the deviations of the R-T and S-T segments are the most conspicuous and most frequent electrocardiographic evidences of recent focal myocardial injury. The deviation of this segment above the isoelectric level in Lead I and a corresponding depression below this level in Lead III are in agreement with the statement of Parkinson and Bedford,<sup>11</sup> Barnes and Whitten,<sup>12</sup> and Barnes and Mann,<sup>13</sup> that occlusion of

the anterior descending branch of the left coronary artery with focal injury chiefly at the apical portion of the left ventricle gives rise to a characteristic  $T_1$  type of curve. In the normal heart of the dog the current of injury supplied by this area of focal necrosis is of relatively brief duration as evidenced by the transient nature of the R-T deviation.

An early marked increase in amplitude of the T-waves, directional changes in the T-waves, characteristically opposed to that of the R-T or S-T deviation, a deep, cove-shaped negativity, particularly in Lead I, and more particularly the successive changes from day to day and from week to week up to the longest period of observation (73 days) may be considered as evidences of reparative processes in the affected myocardial area. Special emphasis must be placed upon the successive changes and the importance of serial study rather than on the appearance of an isolated T-wave. The frequent occurrence of low voltage of the initial deflection in Lead I deserves particular comment in relation to coronary occlusion. Its frequent appearance immediately following occlusion indicates clearly that a previous diffuse fibrosis is not essential for its presence and that coronary occlusion alone may be a factor in its production.

The sequential type of rhythm disturbance following coronary occlusion merits special emphasis. It is obvious that ventricular fibrillation is usually the cause of death in the experimental animal and further that it frequently develops within a few minutes after the artery is occluded. However, in many instances there is an appreciable time interval, usually hours, before ventricular fibrillation sets in, and the probability of its appearance is indicated first by the appearance of isolated premature contractions arising chiefly in the ventricle or nodal tissue, later by ectopic tachycardia, usually ventricular, and finally a brief period of ventricular flutter. The appearance of any of these arrhythmias is therefore of considerable prognostic import.

#### SUMMARY

1. In 50 dogs under full amytal anesthesia and before operative procedures, control electrocardiograms indicated marked normal variations of the T-waves.  $T_1$  was positive in 13 instances, isoelectric in 10, diphasic in 2, and inverted in 25.  $T_1$  negativity was usually accompanied by  $T_2$  and  $T_3$  positivity, but in several instances  $T_2$  and sometimes  $T_2$  and  $T_3$  were also negative. Of the 25 dogs in which  $T_1$  was negative,  $T_2$  was positive in 6 instances, negative in 10, and diphasic in 9.  $T_3$  was positive in 15 instances, diphasic in 4, and negative in 6.  $T_1$  negativity was of variable magnitude, not infrequently sharply pointed and not unlike that described as typical of coronary occlusion. In only one instance was there any deviation of the S-T or RS-T segment of the electrocardiogram.

2. Occlusion of the anterior descending branch of the left coronary artery is attended with characteristic electrocardiographic changes. In 26 of 33 dogs serially studied, deviations of the R-T segment were present, being pronounced in 9 instances and slight in 17 instances. These deviations are most conspicuous in the first two hours following ligation, that is, in the acute stage of myocardial infarction. These changes with associated negativity of the T-wave in Lead I are in accordance with the  $T_1$  type of change as described by Parkinson and Bedford, Barnes and Whitten, and Barnes and Mann.

3. Increased amplitude of T-waves, sharp negativity of the T-waves, particularly in Lead I, and successive directional and amplitudinal changes in the serial of electrocardiograms persisting as long as seventy-three days following ligation were noted. Low voltage of the initial ventricular deflection in Lead I was frequently encountered.

4. Characteristic changes of rhythm were noted following coronary occlusion. Fifteen dogs developed ventricular fibrillation either immediately or within ten minutes following ligation. When ventricular fibrillation did not occur immediately, there was usually a period of normal rhythm for a variable number of hours, following which in eighteen recorded instances, there appeared premature contractions, usually both nodal and ventricular, rarely auricular. This was followed by nodal or ventricular tachycardia and later ventricular flutter, ventricular fibrillation, and death of the animal.

#### REFERENCES

1. Sutherland, F. A., Dial, D., and Harris, B. R.: Observations on Coronary Occlusion. Thermometric Changes, *Proc. Soc. Exper. Biol. & Med.* 30: 1430, 1933.
2. Harris, B. R., Sutherland, F. A., Ramsey, E. M., and Gaiser, D. W.: Observations on Coronary Occlusion: Electrocardiographic Changes, *Proc. Soc. Exper. Biol. & Med.* 31: 222, 1933.
3. Grayzel, D. M., Tennant, R., Stringer, S., and Sutherland, F. A.: Observations on Coronary Occlusion: Chemical and Histologic Changes, *Proc. Soc. Exper. Biol. & Med.* 31: 837, 1934.
4. Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on Experimental Coronary Occlusion. Chemical and Anatomical Changes in Myocardium After Coronary Ligation, *AM. HEART J.* 12: 168, 1936.
5. Kahn, R. H.: Elektrokardiogrammstudien, *Arch. f. d. ges. Physiol.* 140: 627, 1911.
6. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
7. Smith, F. M.: Further Observations on the T-Wave of the Electrocardiogram of the Dog Following Ligation of the Coronary Arteries, *Arch. Int. Med.* 25: 673, 1920.
8. Smith, F. M.: Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch. Int. Med.* 32: 497, 1923.
9. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26: 244, 1920.
10. Oppenheimer, B. S., and Rothschild, M. A.: The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, *Tr. A. Am. Physicians* 39: 247, 1924.
11. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Coronary Infarction, *Heart* 14: 195, 1928.
12. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.

13. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
14. Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *AM. HEART J.* 7: 627, 1932.
15. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
16. Wolferth, C. C., and Wood, F. C.: Use of Chest Leads in Electrocardiographic Studies of Coronary Occlusion, *M. Clin. North America* 16: 161, 1932.
17. Wood, F. C., and Wolferth, C. C.: Experimental Coronary Occlusion, *Arch. Int. Med.* 51: 771, 1933.
18. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
19. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, *AM. HEART J.* 6: 522, 1930-31.
20. Wilson, F. N., and Finch, R.: The Effect of Drinking Iced-Water Upon the Form of the T-Deflection of the Electrocardiogram, *Heart* 10: 275, 1923.
21. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* 39: 1, 1924.
22. Swift, H. F.: Rheumatic Fever, *Am. J. Med. Sc.* 170: 631, 1925.
23. Rothschild, M. A., Sachs, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *AM. HEART J.* 2: 356, 1927.
24. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T-Wave in Rheumatic Pericarditis, *AM. HEART J.* 4: 584, 1928-29.
25. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion: II. Experimental, *AM. HEART J.* 5: 77, 1929.
26. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion: I. Clinical, *AM. HEART J.* 5: 68, 1929.
27. Shearer, M. C.: Plateau R-T in a Case of Lobar Pneumonia, *AM. HEART J.* 5: 801, 1930.
28. Shookhoff, C., and Taran, L. M.: Electrocardiographic Studies in Infectious Diseases, *AM. HEART J.* 6: 541, 1930-31.

# PRACTICAL APPLICATION OF THE METABOLIC EXERCISE TOLERANCE TEST TO THE TREATMENT OF HEART DISEASE\*†

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KATZ, Soskin and their associates<sup>1</sup> have developed a feasible laboratory procedure for estimating, in an objective manner, the functional status of patients with heart disease. This test is based on the excess oxygen consumption accompanying the performance of a standard exercise. When a large group of ambulatory patients were subjected to this test, the functional capacity of the heart as judged from the excess oxygen consumption was found roughly to parallel the clinical assay of the cardiac status. However, subsequent testing by Dr. H. Strauss<sup>2</sup> of a group of some fourteen ambulatory patients with coronary sclerosis and angina pectoris yielded exercise tolerances within the normal range. It seemed evident that the functional capacity of the heart was not the only factor determining the excess oxygen consumption, and further studies were deemed advisable.

In the present study, three patients with congestive heart failure of a degree which demanded rest in bed were tested during their hospital stay.

## REPORT OF CASES

CASE 1.—A pregnant woman with severe thyrotoxicosis, having dyspnea, palpitation, and tachycardia, was tested sixty days after admission with complete bed rest and showed 9.5 c.c. excess oxygen per kilogram meter of work per square meter of body surface.

CASE 2.—A patient with diabetes mellitus, arteriosclerotic heart disease and congestive heart failure had four tests during her stay in the hospital. These were run 1, 4, 9, and 14 days, respectively, after admission. The results ranged between 9.9 and 5.3 c.c. excess oxygen per kilogram meter of work per square meter of body surface, the individual values being 5.3, 7.3, 9.1, and 9.9 c.c. excess oxygen per kilogram meter of work per square meter of body surface.

These values were within or close to the normal range of excess oxygen consumption found previously with this test, viz., 2.2 to 7.5 c.c. excess oxygen per kilogram meter of work per square meter of body surface. The question, therefore, arose as to whether the bed rest which these patients had had prior to their tests could have been responsible for their relatively good exercise tolerance. Evidence suggesting that this was so was obtained in an extremely cooperative patient during her recovery from congestive heart failure which was complicated by a temporary return of congestive failure.

CASE 3.—Mrs. R. M., aged thirty-eight years, was admitted on Nov. 16, 1934, to the Michael Reese Hospital on Dr. Hamburger's service. She was slightly cyanotic,

\*From the Heart Station and the Max Pam Unit of the Michael Reese Hospital.  
†Aided by the F. K. Babson and Max Pam Funds.

extremely dyspneic, and orthopneic. Signs of fluid in the right pleural cavity were present. Râles were heard over the left lung base. The neck veins were pulsating; the liver was down three fingerbreadths below the costal margin and was tender. The heart was enlarged to the right and left, both systolic and diastolic murmurs were heard over the apex. Auricular fibrillation was evident; the average ventricular rate was 94 beats per minute; and the pulse deficit was 8.

The patient gave a history of scarlatinal infection in childhood with no complications. She had no history of rheumatic fever or chorea. Five years before admission she had experienced sudden severe pains in the chest and had a hemoptysis which forced her to go to the hospital where she remained for five weeks. Since then, she had had attacks of palpitation, with increasing ankle edema, orthopnea, and dyspnea.

She was put to bed on admission and received digitalis leaf, 1 grain daily. On November 17 her basal metabolic rate was +31 per cent. On November 18 her dyspnea was less marked. Her exercise tolerance test on this date was 31.1 c.c. excess oxygen per kilogram meter per square meter. The arm-to-tongue circulation time was 26 seconds.

On November 21 she was much improved clinically. Basal metabolic rate was +18 per cent; ventricular rate, 84; pulse deficit, 12; arm-to-tongue circulation time, 25.5 seconds. Exercise tolerance was 16.2 c.c. excess oxygen per kilogram meter per square meter.

On November 22 patient was allowed up in a wheel chair for one hour each afternoon.

Three days later clinical improvement continued. Exercise tolerance was 16.7 c.c. excess oxygen per kilogram meter per square meter.

On November 27 exercise tolerance was 18.6 c.c. excess oxygen per kilogram meter per square meter; ventricular rate, 76 with no pulse deficit; the basal metabolic rate was +15 per cent.

On November 28 patient developed anorexia, was nauseated, vomited, and had diarrhea. The fibrillation of the auricles was still present, the ventricular rate was 64 with no pulse deficit. The patient was put back to bed.

The next day the patient was very apprehensive. The ventricular rate was 80 and the pulse deficit, 6. The exercise tolerance was 35.9 c.c. excess oxygen per kilogram meter per square meter.

On December 2, after four days of bed rest, the patient was clinically better, and subjective symptoms were no longer present. She was more quiet and composed. Ventricular rate was 56; pulse deficit, 6. Exercise tolerance was 24.2 c.c. excess oxygen per kilogram meter per square meter.

On December 5 the patient was much improved and was ready to go home. Exercise was 14.9 c.c. excess oxygen per kilogram meter per square meter.

The next day the physical examination showed auricular fibrillation, and an explosive systolic murmur over the apex was present with  $P_2$  accentuated. Liver dullness extended two fingerbreadths below the costal margin. The liver was not tender. Occasional moist râles were heard at the base of the lungs.

The patient went home, rested a number of hours daily, and continued to take digitalis. She was readmitted two months later for study regarding a total thyroidectomy. At that time there were no signs of congestive failure. She still had auricular fibrillation with an average ventricular rate at the apex of 80. During this stay at the hospital, her exercise tolerance was tested (Feb. 18, 1935) and gave a value of 15.5 c.c. excess oxygen per kilogram meter per square meter.

## COMMENT

The changes in exercise tolerance of this patient are plotted in Fig. 1. While this patient always showed an exercise tolerance definitely outside normal limits, her low values were not far outside the normal range. The observations in this patient are illuminating in showing how labile the exercise tolerance test can be and how closely the exercise tolerance follows the clinical course. In fact, it seems that the exercise tolerance returned toward its stable level before other evidences of clinical improvement were apparent.

This experience suggests that the metabolic exercise tolerance test is not so much a measure of the functional capacity of the heart as it is

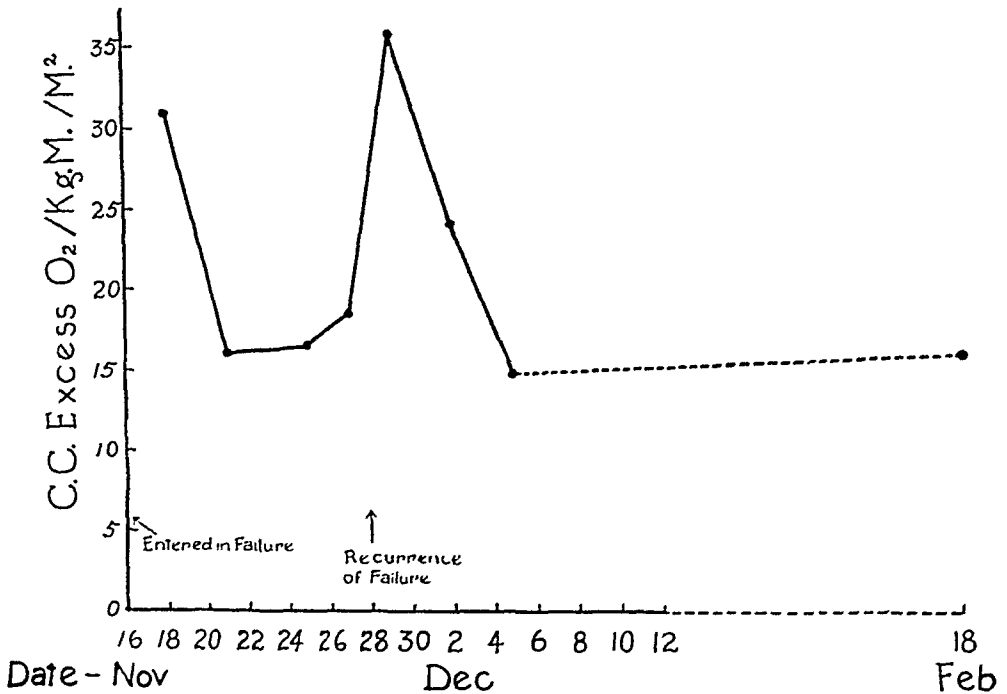


Fig. 1.

an index of how close the patient is to the *limit* of functional capacity at the time of the test. In other words, it is a measure of the functional cardiac reserve rather than of the functional cardiac capacity, if by reserve is meant the difference between the total strain the heart can withstand (its functional capacity) and the strain under which it is working. Thus, the strain upon the heart cannot be ignored in evaluating the significance of the test. A patient with a low functional capacity may show a normal exercise tolerance if his heart has been spared from strain by proper and continued bed rest. On the other hand, a patient with a relatively good functional capacity may show an abnormal exercise tolerance if his heart has been put to undue and continued physical (and/or emotional) strain. In the same patient, no change in exercise tolerance is to be expected if the strain on the heart is reduced

proportionately to the reduction in its functional capacity, nor will the exercise tolerance vary if the strain on the heart is increased proportionately to the increase in its functional capacity.

According to this conception, the test when applied to ambulatory patients has practical utility since it can give the physician information as to how well adjusted the patient's activity is to his functional cardiac capacity. The test when properly interpreted could help the clinician in prescribing the regimen best suited for his individual cardiac patients. A return of the metabolic exercise tolerance to the normal range would justify the trial of an increased work schedule. Especially significant would be an abnormally poor tolerance which would indicate clearly the immediate need of reducing the amount of activity which the patient is allowed.

I wish to acknowledge my indebtedness to Dr. L. N. Katz and Dr. S. Soskin, at whose suggestion this study was made, for guidance and aid in interpreting results.

#### REFERENCES

1. (a) Katz, L. N., Soskin, S., Schutz, W. J., Ackerman, W., and Plaut, J. L.: Arch. Int. Med. 53: 710, 1934.  
(b) Soskin, S., Katz, L. N., Markle, P., and Henner, R.: Arch. Int. Med. 53: 706, 1934.
2. Strauss, Harry: Personal communication.



## Department of Clinical Reports

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### GONOCOCCUS AORTITIS, WITH MULTILOCLAR ANEURYSM AND CONGENITALLY BICUSPID AORTIC VALVE

#### CASE REPORT\*

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INSTANCES of infection of the aorta by the gonococcus are quite rare, only nine cases being found in a recent search of the literature by Aschner.<sup>1</sup> The present case is reported because of the unique combination of a multilocular aneurysm of the aorta with acute vegetative gonococcus aortitis and congenitally bicuspid aortic valve with acute vegetative gonococcus endocarditis.

#### CLINICAL NOTES

The patient (J. E. T.), a white male, fifty-seven years of age, was admitted July 19, 1934, to the Jackson Memorial Hospital, Miami. For three months prior to admission he had suffered with night sweats, weakness, and loss of appetite. He also complained of joint pains, slight swelling of the ankles and occasional nausea and vomiting. Later, nocturia and pain on micturition were noted. There had been a weight loss of 30 pounds (13.6 kg).

*Past History.*—Five months before admission to the hospital he had gonorrhea, for which he had treated himself with injections of argyrol. Otherwise his previous health had been good, except for the usual childhood diseases.

*Examination.*—On admission he appeared quite ill, with temperature 102.4° F., pulse, 108; and respiration, 24. There was slight impairment of the breath sounds over the right chest posteriorly. The heart was within normal limits on percussion; a soft systolic murmur was audible at the aortic valve area, but no thrill was palpable; the blood pressure was 100/70. Otherwise the physical findings were essentially normal.

*Laboratory Data.*—Urinalysis: specific gravity 1.011, slight trace of albumin, no acetone bodies; sediment contained occasional leucocytes, erythrocytes and granular casts. Hemogram: erythrocytes, 3,440,000; hemoglobin, 65 per cent; leucocytes, 18,750, with 85 per cent polymorphonuclears, 12 per cent lymphocytes, 2 per cent basophiles, and 1 mononuclear. The blood Kahn, Widal and agglutination tests for undulant fever were negative. The blood nonprotein nitrogen was 42 mg., the creatinin 1.5 mg. per 100 c.c. Blood culture taken Aug. 29, 1934, showed no growth after twelve days' incubation, but cultures made Oct. 24, 1934 and Nov. 10, 1934, both showed gram-positive biscuit-shaped diplococci. The complement fixation test for gonococci was reported positive on Nov. 14, 1934, by the United States Public Health Service Laboratory, Washington, D. C.

*Diagnosis and Course.*—In view of the evidence of a serious type of infection and the absence of other findings, the tentative diagnosis of gonococcemia seemed warranted because of the recent gonorrheal urethritis. However, no definite diag-

\*From the Jackson Memorial Hospital, Miami.

nosis was reached at first, owing to the early negative blood culture, the absence of an enlarged spleen and the absence of petechiae. The fever was continuous, intermittent and remittent, the fluctuations being from 96° to 102° F., or even 105° F. on some occasions. The patient became weaker, the anemia more marked, so that by November 10 the hemoglobin was down to 32 per cent in spite of his having received three transfusions. The recovery of an organism from the blood morphologically similar to the gonococcus on two occasions later on, and the appearance of petechiae and the presence of erythrocytes in the urine finally determined the diagnosis of gonococcemia beyond reasonable doubt, although more than three months after admission to the hospital.



Fig. 1.—Drawing of heart after opening aorta displaying multilocular aneurysm above, and bicuspid aortic valve below.

The constancy of the systolic aortic murmur and the advent of a rather faint diastolic aortic murmur were the basis for the diagnosis of acute gonorrheal endocarditis, although on November 10 one of us (E. S. N.) made the following consultation note: "Systolic murmur of low intensity over aortic area. Very faint diastolic murmur (aortic). No cardiac enlargement. Pulse 72. Hard to visualize endocarditis in this patient unless primarily mural rather than valvular."

One of us (M. D.) mentioned gonococcus aortitis as a possible diagnosis, basing this thought on the presence of an infectious nidus, which probably was not a valvulitis because of the absence of cardiac hypertrophy and auscultatory findings pointing to the lack of destructive valvular lesion, but considered the likelihood of such a condition rather remote.

On Nov. 16, 1934, the patient became stuporous, Cheyne-Stokes respiration developed, and he expired, nearly four months after entering the hospital, and seven months after the initial symptoms were noted.

#### CONDENSED REPORT OF NECROPSY

Dr. I. Youmans examined the body after embalming. The skin showed small hemorrhagic petechiae scattered over the abdomen, hands, and knees; there was some edema of the legs. Bilateral pleural adhesions of moderate degree and hypostatic congestion of both lung bases were noted. The spleen was somewhat enlarged and showed one small infarct. The capsules of both kidneys stripped easily, and, though no gross infarcts were found, there were minute hemorrhagic areas in the cortex. The liver was enlarged moderately and appeared to have undergone chronic passive congestion. (The heart will be described below.)

Microscopic study of sections from the kidneys showed acute and chronic inflammatory changes, with some hemorrhagic areas and minute abscesses in the parenchyma. Sections from the liver showed hyperemia and cirrhotic changes, and general cell invasion and accumulations of cells approaching small abscess formation.

#### *The Heart and Aorta*

Because structural changes of questionable etiology were found in the aorta the specimen was sent for study to Dr. Clarence E. de la Chapelle, whose gross and microscopic findings are summarized below:

"The *heart and aortic arch* weigh 282 grams (after fixation). The pericardium is smooth and glistening. The chambers and valves of the right side of the heart are normal in all respects, and the pulmonary artery shows nothing remarkable. On opening the left side of the heart, concentric hypertrophy of the left ventricle is apparent, the ventricular chamber being quite small, while the wall measures 22 mm. in thickness at the base and 20 mm. at the apex. The mitral valve is slightly and irregularly sclerosed along its margin, but is otherwise normal and free from vegetations. The chordae tendineae are normal as are also the papillary muscles. The left auricle presents no abnormal features.

"The *aortic valve* is congenitally bicuspid (Fig. 1.), with some sclerosis and calcification of its margin, and some calcification of what is apparently the posterior cusp. The commissure situated posteriorly is widened (5 mm.), the anterior one, however, is normal. The ostium of the left coronary artery, situated in the posterior portion of the sinus of Valsalva of the "posterior" cusp, is large, while the right coronary artery is seen to have a double (congenital) ostium being formed by two small openings about 1 to 2 mm. in diameter located in the anterior portion of the same sinus. The course and appearance of both coronary arteries are normal. The sinus of Valsalva of the other aortic cusp is dilated into an aneurysmal pouch, the interior of which is relatively smooth.

"An aneurysm with a diameter of 28 mm. and a depth of 15 mm. is present in the supra-auricular portion of the aorta, its lower border being 8 mm. above the posterior commissure of the aortic valve. The margin of this aneurysm is smooth, except on the upper border which is ragged and torn, and just beneath the margin fresh vegetative material fills up about one-third of the floor, while the remainder of the floor consists of multiple loculations smooth and free from vegetations, grouped in a rather bizarre fashion, giving a honeycomb appearance.

"Upon cross-sectioning the aneurysm, about half of its wall is seen to be made up by the superior vena cava, the rest by the right branch of the pulmonary artery as it crosses beneath the arch of the aorta. Some of the loculations are thus revealed as smooth small pouches varying in size from a few millimeters to 1 centi-

meter. The rear wall of the aneurysm seems necrotic and a small hemorrhagic infiltration is noted, seen as a discolored area through the endothelium of the superior vena cava. The remainder of the aorta is smooth, with here and there an atheromatous plaque. The supra-avalvular portion is dilated measuring 8.2 cm. in circumference just above the ring of the aortic valve, but the isthmus portion is of normal size, measuring 5.6 cm. in circumference."



Fig. 2.—Locations from which sections were cut: 1, aortic valve; 2, 2', and 2'', aneurysm and adjacent aorta; 3, floor of aneurysm; 4, 5, 6, and 7, aorta.

#### *Microscopic Findings*

"The sites of the most important sections studied are shown in Fig. 2. All sections were stained with hematoxylin and eosin unless otherwise indicated in the descriptions.

*Aortic Valve (Section 1).—*This valve is thickened by hyalinized fibrous tissue and a small area of calcification is visible. Superficially on both the ventricular and aortic aspects of the cusps there is a suppurative inflammatory lesion, appearing as a vegetative process on the inferior aspect, made up of thrombus material with innumerable polymorphonuclear leucocytes, a few lymphocytes, and some clusters of debris and bacteria; chiefly gram-negative cocci, a few gram-negative intracell-

ular diplococci, and scattered gram-positive organisms. (Goodpasture, Brown and Brenn stains.) This acute inflammatory response has apparently involved only the superficial substance of the valve, and even at the base of the vegetation there is no striking cellular response visible, although in the muscular portion (septum of the left ventricle) adjacent to the aortic ring, the leucocytic response is quite intense, and scattered areas of old fibrosis are also visible here.

*Aneurysm and Adjacent Aorta* (Sections 2, 2', and 2'').—The aorta as seen in Section 2 represents a variable picture as the aneurysmal pouch is approached, ranging from cloudy swelling, vacuolization, fatty changes, and nuclear degeneration to complete loss of nuclei and muscle striations. The intima, subintima, and adventitia are involved by a diffuse suppurative process, mostly polymorphonuclear in a nature, but also including some lymphocytes and plasma cells. The vasa vasorum have undergone thickening, but there is no perivascular cellular infiltration to suggest syphilis. Innumerable thin-walled vessels are present in the thin layer



Fig. 3.—Low power photomicrograph of section 2' through floor of the aneurysm.

of tissue which may have been the adventitia and which forms most of the floor of the aneurysm in this section. The pouch of the aneurysm is filled with loose vegetative thrombotic material, including polymorphonuclear leucocytes, lymphocytes, fibrinous débris—a distinct suppurative lesion. A bacterial stain reveals scattered diplococci in this area.

“In Section 2' (Fig. 3) the underlying wall of the aorta has disappeared and the suppuration extends to and even infiltrates the wall of the superior vena cava, producing a panphlebitis including endophlebitis. The latter presents itself as a small vegetative nodule raised above the endothelial surface and made up mainly of leucocytes and occasional plasma cells. Considerable hemorrhage into the suppurative area and engorgement of the thin-walled blood vessels in the poorly organized fibrous tissue is readily visible. The limiting border of one of the large loculations is seen to consist of fibrous tissue in part hyalinized, while adherent to the inner surface of the smaller sac is a wide thrombus composed of débris and bacteria. This area stained with Weigert elastic stain shows destruction and interruption with thinning of the elastic layer of that part of the wall of the superior

vena cava adjacent to the floor of the aneurysm. No elastic fibers are seen in either the septum or wall of the loculation.

"A small part of the right branch of the pulmonary artery is visible in Section 2" immediately adjacent to the thin adventitia of the aorta which appears, still forming the floor of the aneurysm and the smaller pouches. Beyond this point under the overhanging margin of the torn edge of the aorta, the suppurative process is again seen, consisting mainly of leucocytes, erythrocytes, fibrinous debris and bacteria. (Using the Brown and Brenn stain a few gram-negative intracellular cocci are seen scattered about in this suppurative process.) The torn and ulcerated margin of the aorta is inverted in a suppurative vegetative thrombus beyond which an intense inflammatory lesion involves the intima and subintima of the aorta, diminishing in intensity distally. At the point of rupture the media shows marked degeneration with nuclear destruction, swelling and necrosis of the fibers and intense infiltration by leucocytes. A few strands of broken elastic fibers remain scattered throughout and near the mesial portion of the aorta the adventitia is markedly thickened.

"In another section through the floor of the aneurysm (Section 5) a loculation is completely visible, the structure of which is similar to the one just described, the wall consisting of old irregularly distributed connective tissue which has undergone hyalinization at some points. No elastic fibers are found in the wall on using Weigert's elastic stain.

"Sections of the aorta (4, 5, 7, and 7,) 2 to 4 cm. distant from the aneurysm in various directions show variable degrees of atherosclerotic changes in the intima and subintima, with here and there mild intimal cellular response. The media presents cloudy swelling with necrotic nuclei, swollen muscle fibers (many of which have lost their striations), and edema. Some fatty metamorphosis of the muscle fibers of the media is shown with sudan III stain. In some areas there is slight focal cell infiltration of the media consisting of lymphocytes and plasma cells. The Weigert elastic stain shows broken, swollen and granular appearing elastic fibers in these sections. The adventitia here is essentially normal.

"*Other Structures.*—The *mitral valve* shows slight sclerosis and on the auricular surface a mild superficial endocardial lesion extends from the midportion to the tip, made up of a mixture of lymphocytes, fibroblasts, and endothelial cells. No vegetative or thrombotic formation or fibrinoid change is noted, nor are any bacteria seen in this area. The *pulmonic* and *tricuspid valves* are normal in structure. The pericardium is essentially normal. The *left auricle* shows slight sclerosis of the endocardium in some areas, and some cloudy swelling and fragmentation of the muscle. Some sections of the *left ventricle* show degenerative changes in the muscle fibers with swelling and loss of nuclei and striations. Similar changes are visible in the papillary muscles. In other sections the left ventricle shows only irrelevant findings, and the same is true of sections of the right auricle and right ventricle. The left coronary artery shows a slightly irregular intimal thickening by sclerosis and a mild local mononuclear response at one site. Its media and adventitia are normal. The right coronary artery appears normal."

#### ANATOMICOPATHOLOGICAL DIAGNOSIS

Multilocular aneurysm of the ascending aorta with acute vegetative (gonococcus) aortitis. Acute suppurative aortitis. Parenchymatous degeneration of the aorta. Aneurysm of the sinus of Valsalva. Bicuspid aortic valve (congenital) with acute vegetative (gonococcus) endocarditis. Sclerosis and nodular calcification of the aortic valve with stenosis. Double coronary ostium (congenital) of right coronary

artery. Hypertrophy (concentric) of the left ventricle. Acute focal suppurative myocarditis. Focal fibrosis and parenchymatous degeneration of the myocardium. Sclerosis of the mitral valve with early superficial endocarditis. Pleural adhesions. Noninflammatory edema of the lungs. Infarction of spleen. Glomerulonephritis. Chronic passive congestion of liver.

#### COMMENT

The congenital origin of the bicuspid aortic valve is indicated by the finding of only two cusps, without a raphe,\* although serial sections through the valve were not made to establish further the congenital origin of the anomaly. The sclerosis and calcification of this valve may have come from attrition, for the tendency of malformed congenital segments to undergo insidious sclerosis, thickening, and calcification has been emphasized by Abbott.<sup>2</sup> On the other hand, the sclerotic changes in the valve may have resulted from a previous inflammation, possibly bacterial, which involved the valve.

The age of the changes noted in the aorta on microscopic examination indicates that an aneurysm existed for some time prior to the recent and terminal invasion by the gonococcus, *but the actual origin of the aneurysm cannot be stated with certainty*. Dr. de la Chappelle<sup>3</sup> held the opinion, in view of his microscopic findings, that the aneurysm, at least the multilocular formation, was postinflammatory in origin, and pointed out that the absence of elastic fibers in the septums of the loculations also speaks against a congenital origin. It is conceivable, even if not likely, that this individual may have had an infection involving the aorta (as well as the aortic valve as noted above) at some time in his life, producing these changes, although there was no such significant previous illness related by the patient.

Abbott<sup>4</sup> has pointed out that a bicuspid aortic valve is frequently associated with a congenital thinning of the aortic wall, predisposing to the formation of an aneurysm. This author<sup>5</sup> after examining our specimen and sections felt that the main aneurysm was primarily due to a congenital thinning of the right posterior wall of the aorta, the saccular aneurysmal bulging following, the loculi possibly developing as secondary sacculations. However, the absence of elastic tissue in the walls of the loculi was conceded undoubtedly to favor a very early inflammatory origin as far as the *secondary* sacculations were concerned.

That the present involvement of the aneurysmal pouch and aorta, in general, was by direct invasion rather than through the vasa vasorum is suggested by the marked inflammatory changes localized in the intima and the subintima, which areas are supplied by the circulating blood, not by the vasa vasorum.<sup>3</sup> The parenchymatous degenerative changes in the media were probably of toxic origin secondary to the gonococcus, as were the changes in the myocardium.

\*Dr. Abbott noted a possible rudimentary raphe between the right and left anterior sinuses behind the composite cusp. Lack of technical facilities did not permit us to make further study of the point after the method of Lewis and Errant recently emphasized by Bishop and Trubek.

NOTE: Our thanks are tendered Dr. Clarence E. de la Chapelle for his kindness in making a detailed study of the specimen and sections and to Dr. Maud E. Abbott for her helpful suggestions.

## REFERENCES

1. Aschner, P. W.: Gonococcus Aneurysms of the Aorta, E. Libman Anniversary Volumes 1: 75, 1932.
2. Abbott, M. E.: On the Relative Incidence and Clinical Significance of a Congenitally Bicuspid Aortic Valve: With Five Illustrative Cases, E. Libman Anniversary Volumes 1: 32, 1932.
3. De la Chapelle, C. E.: Personal communication.
4. Abbott, M. E.: Coarctation of the Aorta of the Adult Type, AM. HEART J. 3: 392, 1928.
5. Abbott, M. E.: Personal communication.



# A CASE OF PULMONARY EMBOLISM SIMULATING CORONARY THROMBOSIS IN A YOUNG MAN AGED THIRTY-THREE YEARS\*

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## REPORT OF CASE

A WHITE, native American business man, thirty-three years old, complained of gradual onset of dyspnea on exertion which was first noted three weeks previously while mowing his lawn. There was slight cough, without hemoptysis, noted especially when lying flat. The dyspnea was not paroxysmal, and there was no wheezing. He had passed a life insurance examination six months previously. His blood pressure was said to have been low one year before. There was no pain, no heart consciousness, no palpitation.

Careful review of the bodily systems revealed nothing.

His hygienic habits were not remarkable. He had exercised less in the past year but had kept his weight down by dietary restriction. His diet was unusual in that he was very fond of eggs. His business had occasioned nervous strain. His sleep had been somewhat restless for two months.

One year before, the patient had suffered an attack of herpes zoster followed by a small abscess of the abdominal wall under the left costal margin which healed uneventfully. Otherwise the past history was negative.

The family history was negative except that a brother had diabetes.

Physical examination showed a slightly obese young man, quite dyspneic and coughing slightly on the slightest exertion. The left border of the heart was 8 cm. to the left of the midsternal line; the midclavicular line was 7.5 cm. The rate was 100, the rhythm regular. A questionable gallop rhythm was noted. The blood pressure was 110 systolic and 95 diastolic. The chest was clear and resonant. Expansion of the right costal margin appeared slightly less than the left. Examination of the abdomen and extremities was negative.

The hemoglobin was 100 (Talqvist), 128 and 109 (Sahli), the red blood cells numbered 6.2 and 5.4 million per cubic millimeter, the white blood cells 17,000 per cubic millimeter.

The electrocardiogram showed sinus tachycardia, rate 120, late inversion of  $T_2$  and  $T_3$ , a small  $Q_4$  and an upright  $T_4$  (Fig. 1A).

A six-foot film of the heart showed prominence in the region of the left ventricle, but the measurements were within normal limits. There was some density of the hilus shadows thought to be due to enlarged pulmonary vessels. There was a small patch of hazy density in the right midchest just outside the hilus region consistent with consolidation or a small amount of interlobar fluid.

The sputum was negative. There was a negative Neufeld reaction to pneumococcus Types I, II, and III.

*Summary.*—A young male adult came to the office complaining of progressive dyspnea of three weeks' duration, was obviously short of breath, showed a rapid slightly large heart with a suggestive gallop rhythm, a slightly diminished expansion of the right chest. Examination of the blood revealed a leucocytosis and a slight polycythemia. The electrocardiogram was thought consistent with coronary occlusion and

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was considered comparable to that of pulmonary embolism. The absence of any apparent origin for the latter and the gradual onset seemed against such a diagnosis, while the age of the patient and the absence of pain weighed against the former diagnosis. Also considered were primary pulmonary arteriosclerosis and pulmonary neoplasm. On the whole, coronary sclerosis with question of occlusion was thought most likely.

The patient was hospitalized. He gradually grew worse, ran a low fever to 100° F., became slightly cyanotic, complained of pain in the right lower chest and upper abdomen radiating into the right shoulder and scapular region. A pleural friction rub was heard in the right lower chest between the axillary lines. The electrocardiogram on the seventh day in the hospital (Fig. 1B) showed a slight depression

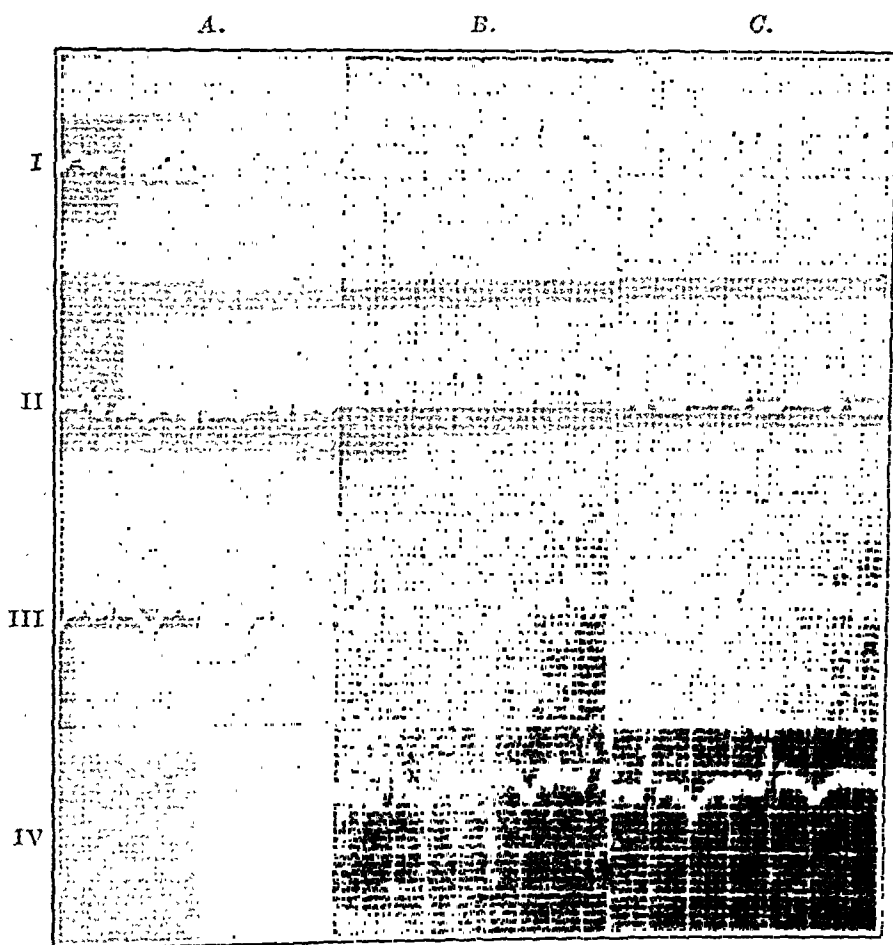


Fig. 1.—Successive electrocardiograms. A, when first seen; B, on the seventh hospital day; C, on the eleventh hospital day.

of S-T<sub>1</sub> and notably different from the first tracing, absent Q<sub>1</sub>, a Deep S<sub>1</sub>, and inverted T<sub>1</sub>. (The patient had received digitalis 0.1 gm. (gr. 1½) three times daily for six days. His weight was 180 pounds.) The electrocardiogram on the eleventh day in the hospital (Fig. 1C) showed no change except inverted T<sub>1</sub> and depressed ST<sub>1</sub>. A loud systolic murmur was heard localized in the pulmonic area. There was a loud superficial sounding, scratchy to-and-fro murmur, similar to a pericardial friction, heard in the third and fourth inter-spaces inside the midclavicular line. Signs of another infarct were found on the left. The patient grew progressively worse and died on the nineteenth day in the hospital.

A diagnosis of multiple pulmonary emboli was made, which emboli were thought to derive from a mural thrombus in the right heart, the result of a coronary oc-

clusion. No other origin for a pulmonary embolus could be found; no immediate or remote symptoms or sign gave the slightest clue.

*Post-Mortem Examination* (J. B. H.).—The body was that of a well-developed and well-nourished white male. Examination was made three hours post mortem. On opening the *pleural* cavities, each was found to contain amber fluid and shreds of fibrin. Partly organized fibrinous adhesions were present between the right lower lobe and the diaphragm and thick layers of fibrin covered the left lower lobe and a portion of the left upper lobe. About 500 c.c. of fluid was present in the right pleural cavity and 1,000 c.c. in the left. Both *lungs* were markedly increased in weight, the right weighing 820 gm., the left 600 gm. Firm, airless, brown and purplish brown areas (1.5 to 4 cm. in diameter) were present in the lower portion of the left upper lobe, the left lower lobe and the right lower lobe. Intervening tissue was crepitant and yellowish gray, except in the left lower lobe where it was atelectatic. Both branches of the *pulmonary artery* were occluded by dull-surfaced, firm, brownish and purplish red blood clot. That filling the right branch was more extensively and firmly adherent to the vessel wall than the clot in the left. Ramifications extended into smaller pulmonary vessels but were blunt and short in the upper lobes, whereas in the lower portions of the lungs they could be traced to the firm brownish purple areas at the periphery. These distal clots were only weakly attached to the vessel walls and could be extruded by slight pressure. The main pulmonary artery contained only fluid blood. Microscopical examination of the large branches of this vessel showed partial organization of the contained clot. This was more extensive in the right. The vessel walls were well preserved and, except for a few lymphocytes in the adventitia, were negative. The firm, rubbery areas in the lungs showed an infarct type of necrosis, with extensive hemorrhage and an infiltration of polymorphonuclear neutrophiles at the periphery. A large artery containing a blood clot showing slight early organization was present in an occasional section. Capillaries in alveolar walls were distended with blood. Some alveoli were dilated and many contained macrophages with included hemosiderin. Occasionally fibrin and partly organized fibrin were found. The alveoli in the left lower lobe were partially collapsed. The *heart* weighed 320 gm. and was of average size. The muscle was firm, brownish red and both grossly and microscopically negative. The myocardium of the right ventricle was markedly thickened (0.5 to 0.9 cm.) but that of the left ventricle was only slightly hypertrophied (1.5 cm.). The endocardium and all valves were negative. The coronary arteries presented a few patches of yellow intimal thickening but were widely patent. The *spleen* presented a slight hemosiderosis. The *liver* was increased in weight to 1,920 gm. and showed accentuated red, central markings. *Gastrointestinal tract, pancreas, kidneys, and adrenals* were negative. The *left common iliac vein* contained a propagated thrombus 5 by 2 by 1.5 cm., unattached to the vessel wall. This was in continuity with a clot filling the *hypogastric vein*. Veins of the *prostatic and vesicle plexus*, on the left, were filled with brown blood clot. This could be pressed from some vessels but in most was firmly adherent to the wall. Microscopic examination revealed varying degrees of organization, and one vessel contained organized, calcified thrombus. Vein walls were negative. Vessels on the right, corresponding to the above, contained fluid blood and a small amount of soft post-mortem clot. The left *seminal vesicle* presented a thick wall and contained clear, viscid fluid. The lumen was dilated and the lining surface smooth. Microscopically the wall was formed of dense hyaline connective tissue and contained patches of calcification. The epithelium was flat, and normal mucosal foldings were absent. Pink-staining masses of coagulated albumin filled the lumen. The other seminal vesicle was negative. *Prostate, testes, and bladder* were negative.

*Diagnosis*.—Embotic and secondary thrombotic occlusion of the main branches of the pulmonary artery; thrombosis of the veins of the left prostatic and vesicle plexus with propagated thrombus in the hypogastric and common iliac veins; old vesiculitis

(left); infarcts of lungs; myocardial hypertrophy (right ventricle); fibrinous pleuritis; hydrothorax; atelectasis (left lower lobe); hemosiderosis of spleen; acute passive congestion of the liver.

#### COMMENT

Pulmonary embolism is readily recognized postoperatively or following phlebitis by sudden onset, dyspnea, with or without pain, cough or hemoptysis, usually with circulatory collapse. The diagnosis may be considered in any female who has borne children or has had pelvic inflammation, because of the possibility of recent or old pelvic phlebitis. But in a previously healthy young man complaining of gradually progressive dyspnea and cough of three weeks' duration and with no history suggesting genitourinary or other disease likely to cause phlebitis, we submit that an unusual myocardial disease of coronary origin, primary pulmonary sclerosis, or even pulmonary neoplasm is more likely. That this reasoning was totally wrong in this case has led us to make this report.

One feature of the first electrocardiogram, namely, upright  $T_4$  with persistence of the Q-wave, led one of us (R. S. P.) to suspect pulmonary embolism, only to rule it out on the above mentioned erroneous reasoning. This change not characteristic of coronary disease was present in two cases of pulmonary embolism reported by McGinn and White.<sup>1</sup> Of the other electrocardiographic signs mentioned by them, namely, prominent  $S_1$ , and low origin of  $T_1$ , gradual "staircase ascent" of  $S-T_2$ , and especially stressed by them,  $Q_3$  and late inversion of  $T_3$ , only the late inversion of  $T_3$  was present. Subsequent electrocardiograms in the present case showed alterations in the T-waves possibly due to digitalis. The absence of  $Q_4$  with a deep  $S_4$  and inversion of  $T_4$  may have been due to faulty application of the electrodes by the nurse or technician while the patient was in the hospital, a common cause of unusual features in Lead IV. In the first tracing the electrodes were accurately placed by one of us (R. S. P.).

#### SUMMARY

An unusual case of pulmonary embolism from unrecognized and asymptomatic pelvic phlebitis in a previously healthy male of thirty-three years is reported.

Accurate electrocardiographic examination with especial reference to Lead IV may be of great importance.

#### REFERENCE

1. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism, *J. A. M. A.* 104: 1473, 1935.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Gupta, J. C.: The Reflex Adjustment of the Circulation and the State of Respiration after Decerebration. *Ztschr. f. Kreislaufforsch.* 28: 492, 1936.

The heart is slower and the mean blood pressure is lower in decerebrate cats and dogs than in narcotized ones. This difference is due to a greater tonic reflex action of the pressor receptor nerves in the former as shown by a lack of difference after resecting these afferent nerves.

L. N. K.

Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Calculation in Cardiac Output From Blood Pressure Measurements Before and After Meals. *Am. J. Physiol.* 116: 551, 1936.

Cardiac outputs can be calculated from the changes in blood pressure and pulse wave velocity following a meal with an accuracy of the same order as that obtained under basal conditions.

Changes in cardiac output after a meal cannot be represented by a simple plateau curve.

The changes in blood pressure and pulse rate are similar to those described by others. The calculated effective peripheral resistance is lowered. Diastolic pressure changes are not a measure of those in effective peripheral resistance. Peripheral dilatation is always associated with a decrease in distensibility of the larger central vessels, as indicated by pulse wave velocities. A constriction of the large vessels is suggested as a possible cause, and presumably these vessels act as an adjustable reservoir.

A method of recording sternal movements is described and is utilized for the timing of the start of cardiac ejection. The relationship of such curves to electrocardiograms is discussed.

The time relations of the electrical and mechanical changes so measured before and after meals are described.

A source of error in the preservation of acetylene samples over mercury is mentioned.

AUTHOR.

Collens, William S., and Wilensky, Nathan D.: New Skin Thermometer for Diagnosis of Peripheral Vascular Disease. *Am. J. Surg.* 33: 157, 1936.

The instrument consists of a mercury thermometer, similar to the ordinary clinical thermometer but with a finer bore to permit a rapid rise of the mercury column. Skin temperature readings, during rising skin temperature, were taken by means of this with the thermocouple as control. The greatest deviation was 1.0° F. The time required for contact of the thermometer with the skin was not given.

H. M.

**Battro, A., and Lanari, A.:** Intra-Arterial Injection of Acetylcholin. *Rev. argent. de cardiol.* 3: 31, 1936.

Intra-arterial injection of acetylcholin (0.04 gram) is an excellent, simple and harmless test to investigate in diseases of the peripheral arterial system in order to determine (a) organic from functional disturbances, (b) the site of the occlusion in cases of organic lesions, and (c) the conditions for collateral circulation. This information is gained through the study of pain, rubescence, and oscillographic variations caused by the drug.

In functional disturbances the changes produced do not differ from those observed in normal individuals. In organic lesions, when the main artery is occluded, the oscillographic index remains unchanged below the site of occlusion, and the conditions for collateral circulation are gauged by the rapidity of appearance, degree, and distribution of the rubescence.

AUTHOR.

**Cushing, E. H.:** Chronic Constrictive Pericarditis, Electrocardiographic and Clinical Studies. *Am. J. M. Sc.* 192: 327, 1936.

Eleven patients with adhesive mediastinopericarditis, upon whom pericardectomy was performed, all had electrocardiograms with QRS complexes of low amplitude. The T-waves were low in voltage. Following pericardectomy the QRS voltage increased in four of seven cases.

AUTHOR.

**Levine, Harold D., and Levine, Samuel A.:** An Electrocardiographic Study of Lead IV With Special Reference to the Findings in Angina Pectoris. *Am. J. M. Sc.* 191: 98, 1936.

Electrocardiographic study was made of forty-four patients who were subsequently examined post mortem. The customary three leads were taken and, in addition, fourth leads with the anterior electrode at the fourth left sternal border and at the apex and with the indifferent electrode on the left leg.

In twelve instances in which the Q-wave was absent in Lead IV, either at the left sternal border or at the apex, infarction of the ventricle was found. Two cases with bundle-branch block and one of tuberculous pericarditis with absent Q<sub>4</sub> showed no infarction.

There were fifteen patients with small Q<sub>4</sub> (2 mm. or less), about half of whom had infarction and the other half did not.

Upright T-waves in Lead IV were found when no infarction was present, and, in fact, where there was no significant heart disease.

In eleven cases in which the heart was normal and in one with posterior infarction, Lead IV was normal.

Evidence is presented to show that myocardial infarction is not uncommon in angina pectoris when there is no clinical evidence of a previous coronary thrombosis. Sixteen of 100 cases showed an absent Q<sub>4</sub> and in eleven of these the customary three leads were essentially normal.

Apart from the changes in Lead IV which occur during the acute phases of coronary thrombosis, we believe that the absence of Q<sub>4</sub> is very helpful in the diagnosis of a previous myocardial infarction, except when bundle-branch block is present.

Lead IV is indispensable in the proper diagnosis of certain cases of heart muscle disease.

AUTHOR.

Levine, Harold D.: The Effect of Various Altered Cardiac Mechanisms on Lead IV. *M. Papers, Christian Birthday Volume*, p. 87, 1936.

Abnormalities generally indicating myocardial infarction may occur in Lead IV in bundle-branch block without infarction.

Auricular fibrillation and flutter per se produce no changes in the QRS-waves of Lead IV.

T-waves are so frequently upright in rheumatic and thyrotoxic heart disease with or without auricular fibrillation that the inference whether or not infarction of the heart is present cannot be drawn from these changes.

The absence of the Q-wave is just as valuable in the diagnosis of myocardial infarction in the presence of auricular fibrillation as with normal sinus rhythm.

In exceptional instances the absence of a Q-wave in Lead IV may be associated with posterior infarction.

AUTHOR.

Graybiel, Ashton, and White, Paul D.: Complete Auriculo-Ventricular Dissociation. A Clinical Study of Seventy-Two Cases With a Note on a Curious Form of Auricular Arrhythmia Frequently Observed. *Am. J. M. Sc.* 192: 334, 1936.

Seventy-two cases of complete A-V dissociation are briefly analyzed. Coronary heart disease was associated in 47 of the patients, congenital heart disease in 4, possible congenital heart disease in 2, rheumatic heart disease in 3, cardiovascular syphilis in 3, and possible chronic diphtheritic heart disease in 4, while the remaining 9 cases were of mixed or entirely uncertain etiology. Two-thirds of the cases (48) were male and one-third (24) were female; it was particularly in the coronary disease and syphilitic groups that the males predominated (36 to 11 in the former and 3 to 0 in the latter).

The heart disease responsible for the block in these cases affects the clinical course, treatment and prognosis far more than does the block itself.

Attacks of dizziness, syncope, or convulsions, symptoms related to the block itself, were present in 44 of the 72 cases; in 4 instances they were the probable cause of death. Adrenalin and ephedrine were the only drugs found valuable in the treatment of these attacks.

The prognosis of those patients in this series with coronary heart disease was generally very poor, although there were striking exceptions; for those with congenital or old diphtheritic heart disease it was good, while for those with luetic or rheumatic disease it was fair.

A form of auricular arrhythmia frequently observed in these cases is discussed.

AUTHOR.

Campbell, Maurice, and Gordon, F. W.: The Quinidine Treatment of Auricular Fibrillation. *Quart. J. Med.* 5: 205, 1936.

The after-results of treatment with quinidine have been followed in two series of patients, one first treated in 1923-28, and the other in 1929-34; almost all have been followed up to December, 1934, or until fibrillation recurred. Quinidine restored normal rhythm in 64 per cent of 135 cases. In 34 per cent it is still maintained after an average period of nearly four years. In 30 per cent it was restored, but fibrillation recurred after an average period of two years. In 36 per cent quinidine failed to restore normal rhythm, or did so for such a short time that it was of no practical importance.

Of the earlier series 25 per cent after nine years, and of the later series 39 per cent after two years still maintain normal rhythm. Quinidine is, therefore,

an effective and often a lasting treatment for auricular fibrillation; its success depends on the careful selection of suitable patients. The duration of fibrillation before treatment, the size of the heart, and the etiology are all important in estimating the chance of restoring normal rhythm and, even more so, of maintaining it for a long period.

Nearly half the cases in which fibrillation had been present for less than a month still maintain normal rhythm, about a quarter of those in which it had been present between one and six months, but few of those in which it had been present for longer. When the heart was only slightly enlarged, 38 per cent, when it was moderately enlarged, 18 per cent are satisfactory, but when it was greatly enlarged only 5 per cent are still satisfactory. Standards for the size of the heart for different body weights have been suggested to help in deciding if quinidine should be used.

The etiology is important and is the main factor in deciding if continuous after-treatment is necessary. In cases in which there is mitral stenosis, the period of restored normal rhythm is not likely to exceed four years. Only 14 per cent of our cases with valvular disease maintain normal rhythm, and in most of these the heart is slightly, if at all, enlarged. Two very successful results were in patients with a history of rheumatic fever but no evidence of mitral stenosis; they have maintained normal rhythm for over eight years without continuing to take quinidine. But in the others with mitral stenosis the average period is as yet only twenty-seven months, and most of them have continued to take it. With appreciable enlargement of the heart, therefore, continuous after-treatment with quinidine is necessary. In those who have relapsed, the average period of restored normal rhythm was nearly two years.

In cases in which fibrillation is present without mitral stenosis or goiter, the selection of cases may be made more leniently, and under favorable circumstances the rhythm may remain normal for ten years or longer. In 39 per cent it is still maintained after an average of five years. In the fifteen who could be classified as having no signs of heart disease except the arrhythmia, it is still maintained in 70 per cent after the same period. After-treatment is not generally needed for more than three months, but, if relapse occurs on omitting quinidine, a second course should be given, and, if successful, quinidine should be continued for longer. In those who have relapsed, the average period of restored rhythm was over two years.

When fibrillation is due to a goiter, nearly all cases should be treated, as, when necessary, an operation will change an unsuitable case into one suitable for quinidine. The duration of fibrillation and even the size of the heart are much less important in this group. A lasting success should generally be achieved, and normal rhythm is still maintained in 80 per cent after an average of forty months. In three patients it has been maintained for nine years and in three others, for four years. With partial thyroidectomy continuous after-treatment with quinidine is not called for. If the patient is treated without operation, the continuous administration of quinidine may be, but is not always, needed.

Thorough digitalization is important before starting treatment by quinidine. Any infection, even a trivial one, may prevent success. Except for the possibility of embolism, which is not a grave risk, serious complications are rare.

Quinidine has an important place in the treatment of auricular fibrillation—provided the cases are carefully selected. The ordinary patient seen in hospital is quite unsuitable; the risk is too great; and, if fibrillation is arrested, it generally returns too soon. Satisfactory results are obtained by paying attention to three main criteria: the absence of congestive failure, of a greatly enlarged heart, or of a long history of fibrillation.



The case is eminently suitable for treatment with quinidine and should certainly be given this opportunity of regaining normal rhythm if there have been no signs of failure, and if the heart is only slightly enlarged (less than 13 cm. maximum transverse diameter in a patient of about 10 stones), and if fibrillation has been established less than one month.

The case is not suitable if there has been gross congestive failure or if any signs of failure persist after treatment with rest and digitalis, or if the heart is greatly enlarged (more than 14 cm. maximum transverse diameter in a patient of about 10 stones), or if fibrillation has been established for six months. The presence of any one of these three usually means that treatment with digitalis should be preferred. In intermediate cases the decision will be made according to how nearly they fall into one or other of these groups.

In cases with mitral stenosis these conditions must be strictly observed. Less attention need be paid to them if fibrillation is due to a goiter, as, if necessary, partial thyroidectomy will convert an unfavorable case into one favorable for quinidine.

AUTHOR.

Gelman, I., and Pusik, W.: The Pathological and Electrocardiographic Characteristics of the Heart in Senility. *Ztschr. f. Kreislaufforsch.* 28: 570, 1936.

Two case reports from Moscow are presented of individuals 112 and 122 years of age! The first had hypertension, cardiac hypertrophy, a four-plus Kahn test, senile dementia, emphysema, and a normal electrocardiogram. He worked on the land until the age of 103 without serious illness and then became an invalid. The second patient worked on the soil until the age of 118. He had had an amputation of the penis for carcinoma at the age of 100 without ill effects and had a long-lasting pyelonephritis at autopsy. An hypertrophied left ventricle was found, and slight coronary sclerosis and emphysema.

L. N. K.

Milew, A.: An Atypical Case of Myocardial Infarct. *Ztschr. f. Kreislaufforsch.* 28: 609, 1936.

A case of myocardial infarct with paroxysmal tachycardia and bundle-branch block is presented. The patient had no pain.

L. N. K.

Sike, H.: Eosinophilic Myocarditis as an Idiosyncratic-Allergic Disease. Frankfurt. *Ztschr. f. Path.* 94: 283, 1936.

After a fair review of the heterogeneity of the pathological picture of myocarditis of uncertain origin (the group which in this country has usually been spoken of as "idiopathic myocarditis"), the author points out that an eosinophilic infiltration has been described a number of times in cases other than those due to diphtheria or trichiniasis. He then describes two patients, both of whom had syphilis, who were treated with moderate amounts of antisypilitic arsenicals, developed severe arsenic dermatitis, and died within a few weeks in the presence of rather abrupt heart failure, dyspnea, pulmonary congestion, cyanosis, low temperature, and faint heart sounds. Neither had cardiovascular syphilis. At autopsy there was found myocarditis characterized chiefly by infiltration of eosinophilic leucocytes, the presence of multinucleated giant cells, broken muscle fibers, and focal necroses. (It should be recalled that eosinophilia is not uncommon in arsenic dermatitis.) After lengthy discussion he suggests that the myocarditis found in these two cases (and in three others in the literature) is the result of an allergic reaction or of an idiosyncrasy of the patients to arsenic.

J. M. S.

Moser, A.: Congenital Absence of the Tricuspid Orifice. *Ztschr. f. Kreislaufforsch.* 28: 521, 1936.

Three cases are reported in which the absence of the tricuspid orifice was associated with a fusion of the two auricles and a defect of the ventricular septum (Wieland's disease). In addition, there was a hypertrophied left and an atrophied right ventricle. The literature is reviewed.

L. N. K.

Gross, Louis, and Fried, B. M.: Lesions in the Auriculo-Ventricular Conduction System Occurring in Rheumatic Fever. *Am. J. Path.* 12: 31, 1936.

One hundred ten human hearts have been examined in order to determine the nature and frequency of the lesions occurring in the Tawara node and bundle of His in rheumatic fever. Sixty of these cases represent active rheumatic fever; 25 cases, inactive rheumatic fever; and 25 cases, nonrheumatic conditions. It has been shown that in active rheumatic fever there occurs a variety of inflammatory and vascular phenomena within the horizontal conduction system as well as in the surrounding tissue. Even when studied in few representative specimens from each bundle, the incidence of these lesions was approximately 66 per cent in the active material. It is probable that a study of more sections would have indicated a higher incidence. Very few of these lesions are of a specific or highly characteristic nature. The inactive rheumatic cases showed few pathological changes. This is in keeping with the functional differences observed as between these two groups. Attention has been called to the high incidence of inflammatory lesions in the collagenous extension of the septum fibrosum and a discussion of the possible mechanisms concerned with the spread of the rheumatic infection to the bundle tissue is given. A description of the topographical relations of the horizontal conduction system in the human heart, together with the findings in twenty-five non-rheumatic control cases, is also given.

AUTHOR.

Friedberg, Charles K., and Gross, Louis: Pericardial Lesions in Rheumatic Fever. *Am. J. Path.* 12: 183, 1936.

Gross and microscopic pericardial lesions are described in sixty-eight cases of active and nineteen cases of inactive rheumatic heart disease. These cases were divided into five clinical groups depending on the course of the disease. The lesions as a whole fell into three characteristic histological patterns which could be correlated with the clinical course. The earliest lesions (first pattern) found in patients who succumbed to a first attack of rheumatic fever consisted primarily of swelling and degeneration of the collagen in the lamina propria, inflammation and vascularization of that layer and subjacent adipose layer, proliferation, desquamation, and pseudogland formation of the epithelial layer, exudation of fibrin, and Aschoff body formation. In the cases with recurrent attacks (second pattern) there were marked thickening of the membranes, universal adhesions and a tendency to obliteration of the pericardial cavity, organization of the inflammatory exudate, and formation of layers. In the chronic slowly progressive and healed cases (third pattern), there were mild lesions characterized by the infiltration of round cells into the deeper portions of the lamina propria and adjacent areas and by increased vascularization and structural alterations of blood vessels. Statistical data from this study indicate the almost invariable presence of pericardial inflammation in rheumatic heart disease. A description is also given of the age period changes in the histology of the normal pericardium.

AUTHOR.

Gross, Louis, and Friedberg, Charles K.: Lesions of the Cardiac Valve Rings in Rheumatic Fever. *Am. J. Path.* 12: 469, 1936.

The authors studied the valve rings of 40 nonrheumatic control hearts and 97 rheumatic hearts. The latter were segregated into six clinical groups according to the presence or absence of Aschoff bodies and the occurrence of one or more attacks of acute rheumatic fever. The valve ring is defined in detail but roughly refers to the most proximal portion of the valve cusp excluding auricular myocardium. The normal rings rarely showed capillaries and never inflammatory cells. The rheumatic rings grossly showed a widening and irregularity in place of the usual fine sharp line of attachment. Microscopically, there were extensive inflammatory lesions which usually involved all of the valve rings. These consisted of extensive infiltration of inflammatory cells, vascularization, edema, scarring, and, except in the last group, Aschoff bodies. These lesions usually involved all four rings, but the pulmonic ring was the most likely to be free. Fibroelastic reduplications were frequently present in the subaortic and subpulmonic angles, and there was frequently inflammation of the intervalvular fibrosa. The valve rings are stressed as strategic sites because it is believed that inflammation of the valves and neighboring sites occurs by spread from the rings.

AUTHOR.

Von Raab, W.: The Central Forms of Arterial Hypertension. *Ergebn. d. inn. Med. u. Kinderh.* 46: 452, 1934.

Separation of the blood vessels from the central nervous system shows that blood vessels have two types of tonus; therefore the vasomotor centers are not alone responsible for high blood pressure. Hypertension occurring during hemorrhage in the brain or resulting from brain tumors may be partly due to some stimulation, partly to direct mechanical pressure on the vascular supply of the vasoconstrictor centers, and partly due to pressure itself on centers, or perhaps it may be caused by destruction of the depressor centers. In poliomyelitis with acute hypertension localized lesions in the medulla have been found. Similar changes seem to be present in cases of encephalitis associated with hypertension. The presence of local circulatory disturbances in vasomotor centers of the brain and medulla in essential hypertension are indicated by the following: (1) frequency of arteriosclerotic changes; (2) occurrence of severe chronic hypertension in patients with marked cerebral arteriosclerosis whose kidneys are not apparently diseased; (3) abnormalities in the arteries in the medulla and pons in cases of essential hypertension; (4) increasing lack of elasticity of the arteries in the brain; (5) increasing sclerotic changes in the smallest brain vessels and narrowing of the cerebral vessels in older people.

The frequent occurrence of hypertension in endocrine disturbances, as suprarenal cortical hypertrophy, pituitary basophilism, and diabetes mellitus, as well as the hypertension associated with polycythemia, may be based principally upon arteriosclerosis in the vasomotor centers and perhaps on direct hormonal stimulation of these centers. Several factors indicate the importance of the central nervous system in the pathogenesis of essential hypertension, such as (1) hypersensitivity of the vasomotor centers to changes in the concentration of carbon dioxide in the blood and increasing response to carbon dioxide of the vasomotor centers in older people; (2) increased sensitivity of the vasomotor centers to decreased oxygen in the inspired air in older persons and persons with hypertension; (3) abnormally marked increase in blood pressure in persons with hypertension and old persons resulting from psychic irritation, muscular exercise, and pain; (4) decrease of an abnormally

high blood pressure during sleep and anesthesia; (5) metabolic abnormalities in essential hypertension, such as elevated metabolism and hyperglycemia, which are probably produced centrally; (6) increased oxygen utilization by the brain in essential hypertension, probably due to a decreased cerebral blood flow; (7) decrease of the blood pressure in hypertension during diathermy of the brain stem; (8) lowering of the blood pressure after lumbar puncture; and (9) depressing effect of adrenalin in hypertension. Essential hypertension appears to be caused mainly by overstimulation and hypersensitivity of the vasomotor centers.

Factors which play rôles in the development of arteriosclerosis in hypertension are heredity and constitution, hormonal influences, infections, and abuses of nicotine and alcohol. The chief factor responsible for organic changes in the vessels of the brain is the content of cholesterol and vitamin D in the diet. These substances are present in butter and milk, animal fat, and the yoke of egg. Some observations on people not living in Europe whose diet is poor in cholesterol and vitamin D show that they have arteriosclerosis and hypertension very rarely. Further statistical investigation is desirable. Some therapeutic procedures, such as administration of sedatives, lumbar puncture, application of diathermy to the brain stem, administration of drugs which increase the circulation in the brain, and perhaps diet, work against the mechanism producing hypertension of central origin; however permanent effects cannot be expected. It is specially important in hypertension of central origin to avoid psychic irritation.

G. R.

Wezler, K., and Böger, A.: The Boundaries of the Arterial Pressure Dome in Man. *Ztschr. f. Kreislaufforsch.* 28: 391, 1936.

The pressure dome converts the intermittent flow from the heart into a constant flow in the capillaries, and it determines the form of pulse in the arteries. The physical methods of measuring volume flow are based on this concept. It is shown that the effective length of the pressure dome can be measured by dividing by 4 the product of the pulse wave velocity in the aorta-iliac tube and the duration between the peak of the primary and diastolic waves in the femoral pulse (which is the pulse wave length).

In determining the pulse wave velocity (a) the length of the tube is measured from the root of the aorta to the point where the femoral pulse is recorded and (b) the time lag of the pulse in the femoral behind the subclavian is multiplied by 1.25.

The length of the pressure dome depends on the body size and is related to the stroke volume. It is longer in tall persons. Its lower limit varies from the iliac to the femoral artery. In hypertension it extends to the muscular arteries. The length of the pressure dome also increases with age. These deductions are based on an analysis of optically recorded subclavian and femoral arterial pulses.

L. N. K.

Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension. *Proc. Staff Meet. Mayo Clin.* 11: 401, 1936.

It is important to know before operation what the effect of the neurosurgical treatment of hypertension will be on the blood pressure. Certain clinical observations are important, but frequently they do not allow accurate prediction. There is stimulation, therefore, to search for a more accurate method of predicting the effect of operation on the blood pressure. Anesthesia induced by the intravenous injection of a solution of pentothal sodium in sufficient amounts to cause a normal

increase in the temperature of the skin of the toes is a safe procedure if the drug is administered expertly. The blood pressure resulting from this procedure constitutes an accurate reflection of that resulting from bilateral resection of the splanchnic nerves and the first and second lumbar ganglions and partial resection of the celiac ganglions and suprarenal glands. Preoperative prediction of the immediate effect of operation on the blood pressure can therefore be made safely and accurately.

AUTHOR.

**Edwards, Edward Allen:** The Orientation of Venous Valves in Relation to Body Surfaces. *Anat. Rec.* 64: 369, 1936.

A seemingly constant orientation of the valves of human veins of the extremities is described. The vein at the site of the valve is elliptical in cross-section, the major axis of the ellipse being parallel to the skin or its tangent. Within the vein at the valve site, the two cusps rise from the long curves of the ellipse so that the aperture between their free margins is also parallel to the overlying skin. The advantage of this arrangement is that the compression transmitted to the veins by overlying structures produces secure apposition of the cusps to each other and thereby insures the competency of the valve.

E. A.

**Ochsner, H. C., and Conner, H. M.:** Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease: Report of a Case and Partial Review of the Literature. *Ann. Int. Med.* 10: 258, 1936.

Among the disorders of lipid metabolism is the so-called essential xanthomatosis with involvement of the skin, mucous membranes, and tendon sheaths, or viscera. The vascular system also may be involved in these xanthomatous changes. A case is reported in which the changes in the vascular system were associated with a lipemia. The patient eventually died from the effect of coronary thrombosis. There was nothing to suggest Gaucher's disease, and Schüller-Christian's, Niemann-Pick's and Tay-Sachs' diseases were readily excluded on the basis of the patient's age. The case was classified as one of essential xanthomatosis with localization primarily in the vascular system.

E. A. H.

**Armentano, L., Bentsáth, A., Béres, T., Rusznyak, St., and Szent-gyorgyi, A.:** Concerning the Influence of Substances of the Flavoral Group Upon the Permeability of the Capillaries—Vitamin P. *Deutsche med. Wchnschr.* 62: 1326, 1936.

The authors expand the preliminary note in *Nature* of July 4, 1936, concerning the actions of these substances and append cases for illustration. It was previously noted that whole lemon juice or paprika would relieve certain cases of purpura which were unaltered by pure ascorbic acid. Several extracts were then made from lemon juice, the various methods of extracting being given in some detail and one preparation was obtained in crystalline form to which is given the name "citrin." These substances were used in treating cases of "vascular purpura;" that is, cutaneous purpuric spots affecting young adults apparently well in other respects. Platelets numbered from 180,000 to 280,000, capillary resistance was low (10 mm. Hg.), capillary filtration was rapid and protein was present in the capillary filtrate. The use of "citrin" brought about disappearance of purpuric spots within ten days, and return of the capillary resistance and other factors to normal. Unfortunately

there is no notation of the number of platelets after treatment. The authors mention four similar cases in which the platelet counts were not decreased and in which the drug was of no use. Last, ten instances of hemorrhagic diathesis occurring during the course of a variety of diseases as chronic infections, nephritis, and diabetes are reported in which immediate, if only temporary, relief was afforded in all instances, even when steady progress of the original disease led to death. Although the data in these last ten cases is insufficient, the results arrest one's attention with regard to possibilities of the drug.

J. M. S.

**Prinzmetal, Myron:** Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association With Sclerodactylia. *Arch. Int. Med.* 58: 309, 1936.

In sclerodactylia the areas of greatest circulatory insufficiency correspond with the areas of greatest shrinkage of skin and subcutaneous tissue. Skin temperature of the digits follows room temperature much more closely than it does in Raynaud's disease without sclerodactylia. Various vasodilatation procedures, including sympathectomy, failed to disturb equality of skin and room temperature. Artificial sclerodactylia was produced in normal fingers by constricting them with pressures between 60 and 90 mm. Hg. Skin temperature, taken through a small opening in the constricting device, closely followed room temperature, and vasodilatation procedures failed to disturb this equality.

It is concluded that arterial occlusive phenomena in sclerodactylia are probably caused by the tight skin and subcutaneous tissue, and that attempts to dilate the vessels in the affected area by heat or sympathectomy do not, and should not be expected to, relieve sclerodactylia. In one patient incision of skin was tried; no retraction of skin edges and no improvement followed. The most rational therapeutic procedure is the use of alternate suction and pressure. This was found to be helpful in some cases.

AUTHOR.

**Galloway, R. J. M.:** The Changes in the Appearance of the Wall of a Muscular Artery Between Diastolic and Systolic Blood Pressures. *Am. J. Path.* 12: 333, 1936.

The number of folds present in the intima and internal elastic laminae of muscular arteries is a criterion for the degree of contraction present in the muscle tissue of the media.

The degree of post-mortem contraction in excised arteries is not uniform. It varies not only in different arteries from the same individual but in different parts of the same segment of an artery. These differences are due largely to differences in stimuli produced in excising the arteries, although other factors also probably play some part.

Relaxed excised arteries, distended by pressures equivalent to at least 80 mm. Hg or more, show a loss of waviness of the intima and of the elastic tissues in the wall. The elastic fibers in the media and in the external elastic lamina lose their wavy contour before the fibers in the internal elastic lamina.

The changes in the artery wall during the passing of the pulse wave probably vary between a moderate folding of the intima and internal elastic lamina at diastolic blood pressure, and a lesser degree of this folding at systolic pressure, a change that may even extend to a complete loss of folds in these layers.

AUTHOR.

Gottesman, J.: Arteriovenous Aneurysm of Hand. *Am. J. Surg.* 33: 323, 1936.

A single case report is given. There was a distinct pulsation over the thumb, thenar eminence, the proximal half of the index finger, and the adjacent palm. Pain at times was severe; bleeding was frequent following trauma. Because of bleeding and infection the thumb and forefinger were amputated. Pathological examination showed the distal phalanx of the thumb and the middle phalanx of the index finger to be permeated by large, thick, anastomosing vascular channels. In most cases it was impossible to identify the vessels as arteries or veins.

H. M.

Theis, Frank V., and Freeland, M. R.: Peripheral Circulatory Diseases. Effect of Alternating Positive and Negative Pressure Treatment on Venous Blood and the Skin Temperatures: Preliminary Report. *J. A. M. A.* 107: 1097, 1936.

Studies were made of the effect of alternate suction and pressure, of heat, and of a combination of the two, on several factors in vascular insufficiency in the lower extremities. Emphasis is laid on skin temperature readings on the toes and on values for  $O_2$  and  $CO_2$  in the blood from the upper part of the saphenous vein of the affected limb. When heat was used, some degree of sweating was usually effected. When suction and pressure was used, it was used for one hour, measurements being taken before and after the procedure.

Reasoning from values obtained for the three variables, skin temperature,  $O_2$  saturation, and  $CO_2$ , the authors conclude that the effect of suction and pressure alone is to increase tissue metabolism rather than to increase blood flow. They base this conclusion mainly on a slightly reduced average  $O_2/CO_2$  ratio in venous blood under suction alone and on an increased average  $O_2/CO_2$  ratio in venous blood resulting from reflex vasodilatation caused by heat. They agree with previous authors that heat should be used with suction and pressure but believe that suction and pressure is effective by its increasing tissue metabolism rather than by its increasing blood flow.

H. M.

Horton, Bayard T., Brown, George E., and Roth, Grace M.: Hypersensitiveness to Cold With Local and Systemic Manifestations of a Histamine-Like Character. *J. A. M. A.* 107: 1263, 1936.

Certain subjects exhibit abnormal local and systemic reaction to cold. The local effects on that part of the skin exposed to cold include redness, swelling, and increased skin temperature on removal. There is flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, a tendency to, or the actual development of, syncope. When a tourniquet is placed on an arm and that hand is placed in cold water, there is no systemic reaction, but one or two minutes after removal of the tourniquet the systemic reactions are more severe than when no tourniquet is used. In six cold-sensitive subjects the same clinical syndrome was produced by administration of histamine. Analyses of gastric free hydrochloric acid before and after eliciting the response to cold showed differences similar to those found by injection of histamine. Attempts to isolate histamine from the blood at the height of a systemic reaction to cold have been unsuccessful and were also unsuccessful when histamine was injected in quantities sufficient to produce shock.

Some of the patients have been susceptible to exposure to cold for many years. Systemic desensitization to cold is accomplished successfully in most patients by frequent short exposure of the hands to cold water. The authors refer to a case in the literature in which a patient was desensitized to cold by administration of histamine. (Bray.)

H. M.

Lederer, Emil: *Studies of the Capillary Circulation. Part I. Basic Principles—the Method. Part II. The Action of Different Drugs Upon the Circulation.* Arch. f. exper. Path. u. Pharmacol. 182: 182 and 363, 1936.

Part I. Studies of the nail beds of twelve children by means of a capillary microscope were made, each on ten or eleven different days. A length of capillary loop 0.4 mm. long was measured out with a micrometer, and the passage of a red blood cell through the capillary was timed by holding down a button connected to a chronometer during its passage. For traversing the 0.4 mm. of capillary from 1.6 to 2.4 sec. were required. Variations in the same child from day to day under similar conditions and at similar times were from 0.2 to 0.8 sec.

Part II. The author then proceeded to study the effect of various drugs. Thyroxin, acetylcholin hydrate, and padutin (a muscle extract) were usually followed by a widening of the capillaries, the appearance of new loops, and an increase in rate of flow, frequently to a point where it was too swift to be timed. It is interesting to note that this occurred in fifteen to thirty minutes after subcutaneous injection of thyroxin in nine of the twelve children. (As is well known, the basal metabolic rate of tissue does not change until much later.) Adrenalin, atropin, and pitressin all slowed the capillary stream, often to the point of complete cessation of flow, and caused disappearance of many capillary loops.

J. M. S.

Faber, B., and Kjaergaard, H.: *X-ray Kymograms of Normal and Pathological Hearts.* Brit. J. Radiol. 9: 335, 1936.

This paper is one of the many which during the last few years have appeared in the European literature as evidence of the wide acceptance which this method of examination is gaining. It comes from the Provincial Hospital of Aarhus, Denmark, and is the report of 1,700 cases which have been analyzed by the authors. They find x-ray kymography particularly useful in the examination of mitral hearts. They emphasize the importance of hardness of the wall of the aorta in interfering with aortic movements, also in syphilitic aortitis which thus may become difficult to distinguish from arteriosclerotic aortitis by this method. They also emphasize the value of this method in differentiating between aneurysm and mediastinal tumor. They have never found a "Type 2" shadow (that is the type in which the waves at the base of the heart are more powerful than those in the apex area) in young persons with normal hearts. This they, therefore, consider evidence of pathology though it need not necessarily represent definite anatomical change in the ventricle of the heart. They have seen it especially in coronary sclerosis and after coronary thrombosis. The paper closes with the remark that they believe that kymography is the future method of x-ray examination of the heart.

J. J.

Beck, Claude S.: *The Heart as a Surgical Organ. With Special Reference to Development of a New Blood Supply by Operation.* Ohio State M. J. 32: 113, 1936.

A brief résumé of surgical procedures useful for the cure of heart disease and wounds is presented. The author then proceeds to explain the basis for surgical treatment of coronary sclerosis by implantation of peccary muscle grafts to the wall of the heart. He describes the experimental development of the operation of animal- and then on four patients.

He believes the experimental results on animals and those obtained in the four patients indicate that coronary sclerosis may be treated satisfactorily by such an operation.

H. McC.



Griswold, R. A.: Chronic Cardiac Compression Due to Constricting Pericarditis. J. A. M. A. 106: 1054, 1936.

In a patient with chronic cardiac compression caused by scar (the Pick syndrome) complete relief was obtained by resection of the constricting scar.

The roentgenokymogram is of value both as a positive diagnostic measure and as evidence of the efficacy of pericardiectomy.

There are advantages of decompression of the heart during the postoperative period by drainage into the pleura.

Several points in the technic of the operative procedure are emphasized, especially in the dissection of the scar from the heart.

AUTHOR.

Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity. Ann. Surg. 104: 339, 1936.

The unsatisfactory end-results from cervicodorsal sympathetic ganglionectomy for vascular spasm (Raynaud's disease) is attributed to degeneration of the postganglionic fibers and consequent sensitivity to adrenalin when this takes place. A modified dorsal sympathectomy for relief of vascular spasm is described in which only preganglionic fibers are sectioned and the postganglionic fibers are left intact. This operation has been carried out in thirty-three upper extremities in twenty-three patients. Eight of the cases had an associated scleroderma with fibrosis of the soft tissues of the fingers and often with destruction of the terminal phalanges. Clinical results have been extremely satisfactory, as there has been no evidence of recurrence of vascular spasm. The longest interval since operation is eleven months. Three of the cases were tested by the intravenous administration of adrenalin in a dilution of 1 to 250,000. The surface temperature fall in the upper extremities was comparable to that obtained in a sympathectomized foot. If regeneration of nerve fibers at a later date does not cause recurrence of vascular spasm, this should be a satisfactory procedure for eliminating vascular spasm in the upper extremities.

E. A. H.

Blum, Lester, and Gross, Louis: Technic of Experimental Coronary Sinus Ligation. J. Thoracic Surg. 5: 522, 1936.

Coronary sinus occlusion in the dog's heart produces a rapid increase in the extent of the coronary tree and in the intramyocardial collaterals as determined by the injection technic. In the majority of dogs' hearts thus prepared it is difficult or impossible to induce infarction by subsequent acute occlusion (division between ligatures) of the left anterior descending branch approximately 2 cm. below the aortic ostium of the left coronary artery. A description is given of the technic which we have found most satisfactory for the production of coronary sinus occlusion in the dog's heart. We believe that the method, with variations in technic in keeping with a somewhat different anatomic arrangement, may be applicable to the human heart and have therefore presented the procedure in this report.

AUTHOR.

White, James C.: Surgery of the Sympathetic Nervous System. J. A. M. A. 107: 350, 1936.

Uniformly successful results have been obtained in all 18 cases of Raynaud's disease of the lower extremity by resecting the second and third sympathetic ganglions. Up to six years after operation results are as satisfactory as on the day of discharge. In the arm the operative results have, until recently, been far

less satisfactory. Six months after resection of the upper two thoracic ganglions (ten cases), or of these two and the inferior cervical ganglion (eleven cases), there was little improvement. The operation which proves to be the one of choice is that of cutting the sympathetic chain below its third thoracic ganglion and severing the communicant rami from the second and third intercostal nerves. This operation has now been performed twenty-eight times on eighteen patients, and observations over a period of one and a half years have demonstrated that the lasting increase in blood flow in the arm after this operation can be as great as in the leg.

Sympathectomy for other diseases than Raynaud's is discussed.

H. M.

**Brown, W. S.:** Successful Operation for Mesenteric Vascular Occlusion. *Am. J. Surg.* 32: 499, 1936.

A brief review of the literature is given. The rare cases of successful surgical intervention are described. In the author's case a large portion of gangrenous bowel, evidently ileum, was removed. The bowel was reunited. The microscopical report was acute hemorrhagic infarction with necrosis and acute purulent inflammation of the intestine. No cause for the occlusion was given.

H. M.

**Bullrich, R. A.:** Treatment of the Pain of Angina Pectoris With Cobra Venom. *Rev. argent. de cardiol.* 3: 111, 1936.

Because of the analgesic properties of cobra venom, it was used to relieve pain of patients suffering from angina pectoris. The results obtained in ten patients seem to be quite encouraging. In all cases pain was considerably decreased and the work-performing capacity was considerably increased; patients who could not walk more than 30 meters were able to walk a kilometer or more without trouble. This is a symptomatic treatment which has no appreciable effect on blood pressure or the electrocardiogram. The favorable effects disappear when the treatment is discontinued. To begin, the intravenous injections should be made every other day; once the condition of the patient has improved, the injection should be repeated every four to five days. No accident ascribable to cobra venom was recorded in any case.

AUTHOR.

## Book Reviews

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VASCULAR DISORDERS OF THE LIMBS. By Sir Thomas Lewis, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London; Honorary Physician to the Ministry of Pensions; Consulting Physician, City of London Hospital; Fellow of University College, London. New York, 1936, The Macmillan Company, Cloth, 8vo, 111 pages, \$2.

This excellent volume has been written by an internationally recognized authority on many phases of circulation. Most of the material is from papers by the author and his associates previously published in the journal *Heart* and in the first two volumes of *Clinical Science*. The book, as the author states in the preface, is not a comprehensive account of vascular disorders of the limbs, and its value is somewhat lessened by the absence of controversial data and of a bibliography.

The author believes that "the time is opportune to attempt to outline conceptions of certain peripheral disorders of the circulation in a way that may prove useful to those engaged, not in research, but in practice." There is some doubt that the volume will serve this purpose since diagnosis and treatment are presented very incompletely and inadequately. The presentation is essentially that of a clinical physiologist interested in mechanisms rather than in diseases. The volume presents a definite contribution in this regard, as demonstrated in the chapters, "The Circulation in the Limb and Its Testing" and "Effects of Circulatory Arrest." In the chapter, "Embolism and Thrombosis of Main Arteries," however, the explanation of the marked diminution in circulation following arterial embolism is not altogether convincing. The effects of embolism on the circulation appear to be more profound than those of simple ligation or compression of an artery, and this needs further consideration. The short chapter, "Post-Ischemic Contracture: Intermittent Claudication," appears complete, but the thirteen-page chapter, "Arteriosclerosis; Thrombo-Angiitis Obliterans," is deficient in certain respects. The chapters, "Vasoconstriction: Local Arterial Spasm" and "Spasmodic Arterial Obstruction; Raynaud's Phenomenon," are clearly and concisely written. The explanation, however, of the uniformly good results which follow sympathectomy for Raynaud's disease of the lower extremities, in contrast to occasional failure of good results to follow sympathectomy for Raynaud's disease of the upper extremities, is not entirely convincing. Recent investigative work on this problem is not mentioned. The author believes that Raynaud's disease is a manifestation of local fault in digital arteries and that it is not attributable to overactivity of the sympathetic nervous system.

The chapter, "Gangrene (Bilateral Forms; Cervical Rib; General)," is well presented. The one, "Vasodilatation; Flushing," indicates that much remains to be done to clarify the subject. The term "erythrocyanosis" is used in place of the commonly used terms "cutis marmorata" or "livedo reticularis," but does not appear to be a better designation. The reader may be disposed to question the accuracy of the statement, "It came in with short skirts and thin stockings and will go out with them." The author raises objection to the term "erythromelalgia," and "erythralgia" is suggested as more appropriate. Since the term "erythromelalgia" is an accepted medical term, it would seem to the reviewer advisable to retain the latter.

No mention of the vasodilating syndrome frequently associated with polycythemia is made. Trial of sympathectomy is recommended for "erythralgia," but no reason is given for this recommendation, and no results are mentioned. This approach ap-

appears illogical to the reviewer since pain in this condition is aggravated by increasing the temperature of the skin, an anticipated result of successful sympathectomy. The final chapter, "Vascular Disorders in Diseases of the Nervous System," is clearly written and contains much valuable information.

This book constitutes an outstanding volume of explanations of the mechanisms of circulatory disturbances although it seems of limited value to the physician whose chief interests in peripheral vascular diseases are diagnosis and treatment. It is heartily recommended to every student of vascular diseases, since within its covers are to be found explanations of many of the puzzling phenomena observed in abnormalities of peripheral arterial circulation. It is the sort of work which can be read more than once with pleasure and referred to on numerous occasions with profit.

THE CLINICAL USE OF DIGITALIS. By Drew Luten, M.D., Springfield, Ill., 1936. Charles C. Thomas, 226 pages.

Those who are familiar with Dr. Luten's splendid work upon digitalis will be gratified to know that he has written a book upon its clinical use. They will welcome any work bearing his name with eagerness and confidence, nor will they be disappointed. He begins the preface of this volume with the following sentence: "Not many years ago there were published two classical works on digitalis, each a splendid epitome." Presumably he refers to the admirable work of Robinson and of Cushny, whose books appeared in 1923 and 1925, respectively. It is safe to say that future writers upon this subject must refer to three classical works, for the present volume more than measures up to the high standard of its predecessors.

As the title indicates, this is primarily a study of the clinical use of the drug, but all relevant experimental work has been included in the discussion of its action. It is essentially a summary of all the important work of the past ten years in this field, interpreted by one of the acknowledged authorities in the light of his own wide clinical experience. While most of his references are to work of the past decade, he has not hesitated to make use of important contributions during the preceding quarter century, and some of the most fascinating pages in the book are those devoted to the interpretation of cases reported by Withering and by Mackenzie. He states that he has made no attempt to harmonize conflicting opinion, but he has demonstrated convincingly that authoritative opinion is already in harmony upon almost all the essential points.

There are too many important chapters to permit comment upon all of them. There are few physicians, even among those who specialize in diseases of the heart, who cannot read the book with profit as well as with great pleasure. To those who have worked in this field, perhaps the most important chapters are those dealing with the effect of digitalis upon the ventricular muscle and with the newer views relating to the level of optimum effect and the doses required to produce it. The author brings forward evidence from many directions in support of the increasingly prevalent conception that the tachycardia commonly observed in cases of auricular fibrillation with heart failure is a result of the failure rather than a cause of it. "This conception explains the slowing from digitalis as due in large part at least to the beneficial effect which the drug is known to exert on the ventricular muscle regularly in cases of heart failure, and makes unnecessary the hypothesis that digitalis block depends solely upon a depression of conduction in the A-V tissues." To those unfamiliar with recent work upon digitalis, the amount of evidence supporting this view will be surprising. His comments upon the common practice of regarding auricular fibrillation in itself as an indication for administration of the drug are forceful and wise. He lends the weight of his authority to the current belief that digitalis increases the efficiency of a failing myocardium by enabling it to perform its work with a smaller expenditure of energy. He properly emphasizes the uselessness of the

drug in cases of toxic auricular fibrillation without heart failure and in cases of peripheral circulatory failure; he shows clearly that it should not be administered in cases of shock, septicemia, pneumonia, and other acute infections. The sections relating to the therapeutic zone of digitalis action and the differences in dosage required for different levels of optimum effect are extremely important.

The longest chapter in the book is that upon dosage and method of administration; to these important matters the author devotes sixty-four pages, every one of which is important. If every practitioner could be required to read this one chapter thoughtfully and repeatedly, the improvement in the therapeutic use of digitalis would be enormous. There is no aspect of its therapeutic or toxic action that is not fully and wisely discussed.

The book closes with a quotation from Wenckebach: "Digitalis treatment is one of the most important and serious duties of the general physician; it demands a great deal of skill, power of observation, keen interest, and experience. A long life is too short to learn enough about this wonderful drug." To the writing of this book, Dr. Luten has brought in abundant measure the requisites mentioned by Wenckebach. There is not a page that does not bear witness to his wide experience, his excellent clinical judgment, and his deep interest; there are scores of paragraphs that could have been written only by a wise, kind, experienced physician whose first concern is for the welfare and comfort of his patients. His book takes its proper place on the shelf with those of Cushny and Robinson as the latest in a series of splendid critical reviews. Because it is the latest, because it includes so much work that is new and of fundamental importance, and especially because of the author's distinction, wisdom, and clarity of expression, it stands, in the opinion of this reviewer, as the finest work upon digitalis available today.

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### Books Received

KLINIK UND THERAPIE DER HERZ-KRANKHEITEN UND DER GEFÄSS-KRANKHEITEN. Vorträge für Praktische Ärzte. Von Privatdozent Dr. D. Scherf. Dritte verbesserte und Vermehrte Auflage. Pp. 290. Mit 10 Textabbildungen. Wien: Verlag von Julius Springer, 1936.

OVER VENTRICULAIRE EXTRASYSTOLEN EN HARE LOCALISATIE. PROEFSCHRIFT. Ter verkrijging van den graad van Doctor in de Geneeskunde aan de Hoogeschool te Batavia, op Gezag van den Voorzitter der Faculteit, Dr. B. J. van der Platts, Hoogleraar in de Faculteit der Geneeskunde, tegen de Bedenkingen van die Faculteit te Verdedigen op Vrijdag 29 Mei 1936, des Voormiddags 12 Uur. By Cornelis Johannes Storm. Pp. 193. Paper. G. Kolff and Company. Batavia-C. 1936.

ELECTROCARDIOGRAFÍA PRÁCTICA. By Luis Hervé L. Ayudante de la Catedra de Patología Médica de la Universidad de Chili. Pp. 69. Paper. Libreria e Imprenta "Artes y Letras"; Santiago de Chili; 1936.

ROENTGENKIMOGRAFÍA CONCÉNTRICA. By Alberto C. Morelli. Instituto de Radiología; Profesor Carlos Butler. Pp. 34; 32 plates. Montevideo. 1936.

CARDIOPATIAS CONGENITAS. By Ramon Valdivieso D., Profesor Agregado de Terapéutica, and Domingo Urrutia M. Ayudante de Clinica Médica. Prologo del Prof. E. Gonzalez Cortes. Pp. 158; 48 illustrations. Paper. Santiago de Chili; 1936.

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